An Analysis and Evaluation of the Development of the QRD Human Product Information Template used in Package Leaflets

Dissertation

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Anna Wolf

from Cambridge, Great Britain

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1st Examiner: Prof. Dr. Harald G. Schweim

2nd Examiner: Prof. Dr. Ulrich Jaehde

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Contents list

List of abbreviations

ACE inhibitor	Angiotensin-converting-enzyme inhibitor
ADEC	Australian Drug Evaluation Committee
AMG	Arzneimittelgesetz (German Drug Law)
AMIS	Arzneimittel-informationssystem (comprehensive drug information system)
AMZV	Arzneimittel-Zulassungsverordnung (Marketing Authorisation Regulations in Switzerland)
APAC	Australian Pharmaceutical Advisory Council
ASMI	Australian Self Medication Industry
ATC code	Anatomical Therapeutic Chemical code
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)
BPI	Bundesverband der Pharmazeutische Industrie (German Pharmaceutical Industry Association)
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CHMP	Committee for Medicinal Products for Human Use
CMDh	Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human
CMI	Consumer Medicine Information/Consumer Medication Information
CPI	Consumer Product Information
CVM	Center for Veterinary Medicine
DC	Decentralised
DE	German
e.g.	For example
EC	European Commission
EEA	European Economic Area
EEC	European Economic Community
EMA	European Medicines Agency
EN	English
EPAR	European Public Assessment Report
et al.	*et alli* (and others)
etc.	et cetera

EU	European Union
FDA	Food and Drug Administration
HWG	Heilmittelwerbegesetz (German drug advertisement law)
IKS	Interkantonale Kontrollstelle (Intercantonal office for the control of medicines in Switzerland)
Info	Information
KPAV	Komplementär- und Phytoarzneimittelverordnung (Ordinance of the Swiss Institute of Therapeutic Products concerning simplified Marketing Authorisations for Complementary and Herbal Medicinal Products)
MAH	Marketing Authorisation Holder
MCA	Medicines Control Agency
MDA	Medical Devices Agency
MedDRA	Medical Dictionary for Regulatory Affairs
MedGuide	Medication guide
Medsafe	Medical Devices Safety Authority
MHRA	Medicines and Healthcare products Regulatory Agency
min.	Minimum
max.	Maximum
MR	Mutual recognition
n	Number
N.B.	*nota bene* (note well)
NCPIE	National Council on Patient Information and Education
NDPSC	National Drugs and Poisons Scheduling Committee
No.	Number
n.s.	Not significant
NSAIDs	Non-steroidal Anti-inflammatory Drug
NSAR	Nicht-steroidale Antirheumatika (non-steroid antirheumatic drug)
OTC	Over-the-counter
p	Probability
PDF	Portable Document Format
PHARM	Pharmaceutical Health and Rational use of Medicines
Ph. Eur.	Pharmacopoea Europaea
PI	Product Information
PIL	Patient Information Leaflet
PPI	Patient Package Insert

PRAC	Pharmacovigilance Risk Assessment Committee
pt	Point
QRD	Quality Review of Documents
QUM	Quality Use of Medicines
Rx	Prescription only medicine
SHP Text verification tool	Schlafender Hase und Partner text verification tool (software programme)
SmPC	Summary of Product Characteristics
SOC	System organ classes
SPSS	Statistical Package for the Social Sciences (software programme)
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
TGA	Therapeutic Goods Administration
UK	United Kingdom
VAM	Verordnung über die Arzneimittel (Pharmaceuticals regulation)

1. Introduction

Package leaflets enclosed in medication packages are an important source of information for patients or carers about a particular medicine, whether prescribed or bought over-the-counter[1-3], and should be read before starting treatment and while taking the medication. In addition to providing vital information on indications, contraindications, side effects of the medication, they should also motivate patients to actively participate in their treatment[4].

Improved levels of patient satisfaction have been recorded for patients who received a package leaflet with their medicine[5]. They also improve patients' knowledge of how to take their medicines correctly[5], raise awareness of potential side effects[5,6] and generally improve compliance[7]. One study showed that patients who had received a patient package leaflet reported the same number of side effects as those who had not, but those who had received information were more likely to attribute the experienced reactions to the drug whether the particular side effect was listed or not[6]. However, it has been reported that the patient information leaflet is read by only about 70 - 80 % of patients[1,8] and few request more specific information on their own initiative[9]. It is well known that patients forget or misunderstand much of what is said during consultation with a doctor or pharmacist and it has been found that on average patients had forgotten half of what the doctor told them within 5 minutes of leaving the surgery[10]. A survey with 154 patients showed that although 90 % received verbal information about the treatment regimen, fewer were told how to take the drug or the duration of treatment[9]. The package leaflet is therefore a vital source of information for when the patient returns home following a doctor's consultation[9]. The situation does arise, however, that many patients are subsequently deterred from taking the medicine as the content of the leaflet made them afraid of the treatment[1,8,11]. Specialists have reported that patients frequently have less confidence in their medicine after reading the package leaflet[12]. The consequence of 'less confidence' in a particular medicine due to the complex and detailed information contained in a package leaflet can lead to non-compliance which can have major negative health and economic implications. On one hand this may be via product loss, as shown by a German study in 1988 and repeated in 1998 which revealed that, although prescription charges had increased during the 10 year period, that the amount of unused drugs brought back to the pharmacies had actually increased[13]. On the other hand, non-compliance can also indirectly have monetary effects through the complication of disease management[14]. Non-adherence is multi-faceted in the home-setting and often involves using more or less than the prescribed dose, completely not taking certain medicines, taking an extra dose, using an unauthorised medication or taking medication at the wrong time[15]. Although a patient's ability to abide by a certain prescribed treatment regime may be compromised if they cannot understand basic information about the prescribed medicine, other factors such as the perceived severity of the illness and social circumstances may also have an effect[15]. Not understanding how to take a medicine properly can also lead to avoidable and possibly serious side effects occurring. In a

large scale study on adverse drug reactions as the cause of hospital admission in the United Kingdom, it was shown that up to 70 % were either possibly or definitely avoidable[16]. Incorrectly used drugs are also more frequently involved in adverse drug reactions than those which are correctly used[17]. Improper use was caused by drug interactions, off-label use, incorrect duration and inadequate dosage and contraindications. Reading the package leaflet is therefore vital for safe and effective medication use.

Therefore, the package leaflet must be understandable to a wide spectrum of ages and for all levels of education, but one survey showed that one in five users found them to be not comprehensible[18]. This is a problem which has been identified in the majority of package leaflets. Regardless of the focus in the package leaflet, they require relatively high reading skills that may not exist in a large proportion of their target populations[19]. Many of the terms included in a package leaflet are also not clear enough for a patient to understand, for example 'high doses' or 'long term use'[20]. Not all sections of the package leaflet are of equal comprehensibility for the user. In a Swedish study of 30 randomly selected leaflets, it has been found that although patients could recognise and comprehend various information items in the information leaflet, certain sections, namely 'risks of interactions' and 'contraindications' were poorly understood[21]. This was suggested to be due to the complexity of the information contained in these sections. A further study in Germany to assess patients' knowledge on anticoagulants also revealed that drug-drug and drug-food interactions were least understood[22].

Some sections of the package leaflet are generally considered to be less important than others by the reader, for example, the names and addresses of the pharmaceutical company and manufacturer[23]. In contrast, the indication, dosage instructions and side effects were classed as 'very important'. Readers of package leaflets in Belgium were found to focus mainly on adverse effects (88 %), how to take the medicine and how much to take (85 %) and contraindications (82 %)[8]. A study in which patients were asked to put the importance of the sections of the package leaflet in order of precedence showed that the indication should start the leaflet followed by dose instructions, composition, warnings for use, contraindications, interactions and side effects[23]. This does not completely match the legally defined sequence of sections, as using a logical order requires that contraindications and special warnings must be provided before patients use the dosage instructions[23]. However, the current order of information does better reflect patients' requirements than the version before Directive 2004/27/EC[24] came into force[12].

The content and presence of a package leaflet for a particular medicine was originally determined by the national ruling of the country where it was brought into circulation. This later changed for countries in the European Union (EU) as European legislation was put into place to govern the content and order of information. This marked a major change in the status of the package leaflet in the affected countries. In

1992, the European Community adopted Directive 92/27/EEC[25], which stated that a patient information leaflet (PIL) must be provided with all medicines distributed within the European Union. This legislation was implemented on January 1st 1994 and made the presence of a package leaflet mandatory from January 1999. Package leaflets in some European countries such as Germany had been firmly established since the 1960s, but other countries introduced them comparatively recently. In Belgium, regulations for the mandatory inclusion of a package leaflet had existed since 1984[26] and in France since 1985[27], while the United Kingdom only made them compulsory in 1999 due to European Legislation. Outside the EU, in Switzerland the presence of a patient package insert (PPI) was made a requirement from January 1st 1989[26]. In Australia, consumer product information (CPI) had to be provided for all new drugs by January 1993 and for all existing drugs by January 2002[28]. During the late 1960s, the FDA in the United States of America first introduced patient package inserts but only for certain asthma medications and oral contraceptives[27]. It was only in 2006 that a major revision regarding patient package insert guidelines was made by the FDA.

Although package leaflets were already in use in the 1960s in Germany, original German Drug law (Arzneimittelgesetz) from 1961[29] only required that the name of the medicine and manufacturer, contents of the packet, pharmaceutical form, application method and active ingredients had to be noted on the outer packaging and container, meaning at this time that only certain companies provided a package leaflet with their product. In 1973, the German Pharmaceutical Industry Association (*Bundesverband der Pharmazeutische Industrie* (BPI)) published a guideline regarding package leaflets which was made effective in 1974[30]. This guideline was largely implement into German Drug law from 1976[31], where § 11 made inclusion of a package leaflet mandatory, although its content was intended for patients, doctors and chemists. This was found to cause great difficulties in comprehension by the patient due to the use of the specialist medical terminology in these leaflets[4]. A separation of information for patients and healthcare professionals only came about in 1986 through application of further changes in national drug law[32].

Directives adopted by the European Community require European Member states to implement their provisions nationally. The European Directive 65/65/EEC[33] from January 1965 provided the first laws within the European Union for the production and distribution of medicinal products in order to safeguard patient health. As already stated above, the inclusion of a package leaflet was not mandatory at this time although the particulars which had to appear on the containers and outer packages of medicinal products were mentioned in Articles 13 - 20. Directive 65/65/EEC[33] was amended in 1975 by Directive 75/319/EEC[34]. It was noted in Article 6 that, where a leaflet is enclosed, all information in the leaflet must be provided in accordance with Article 4 of Directive 65/65/EEC[33]. Minimal criteria were defined in Article 6 for the contents of the package leaflet, such as therapeutic indications, contraindications and

directions for use of the product although its presence was to be decided by the relevant member state. Directive 89/341/EEC[35] amended directives 65/65/EEC[33] and 75/319/EEC[34] and the new subparagraph in Article 6 stated *'The inclusion of a package leaflet in the packaging of medicinal products shall be obligatory unless all the information required by this Article is directly conveyed on the container itself and the outer packaging*'.

With the introduction of European Directive 92/27/EC[25] in 1992, further particulars to be described in the package leaflet and on the outer and immediate packaging were defined. Article 7 determined the order and contents of the package leaflet and stated that symbols and pictograms could be used in the package leaflet to clarify certain information, but all elements of a promotional nature must be excluded. Article 8 stated that '*The package leaflet must be written in clear and understandable terms for the patient*'[25]. In Article 12 of this directive it was announced that the Commission was going to publish guidelines, amongst others concerning especially '*the legibility of particulars on the labelling and package leaflet*'. It was originally planned in Article 12 (2) that these guidelines would be adopted in the form of a directive but this never happened. Rather, the first Readability Guideline was published after approval by the Pharmaceutical Committee of the European Commission in September 1998[36] with the proposed date for coming into operation in January 1999. As it never became enforced as a directive it remained a 'Guideline' according to Article 249 of the 'Consolidated versions of the treaty on European Union and of the treaty establishing the European community' where it is defined that recommendations and opinions have no binding force[37]. The Readability Guideline was however still updated in January 2009[38]. The purpose of the guideline was to lay down general principles to help pharmaceutical companies make the labelling and information in the package leaflet legible and comprehensible for the patient. The first Readability Guideline edition in 1998 contained a model template for the package leaflet and both editions included a means of testing readability to examine whether the user can find and understand appropriate information in the leaflet, and act on it accordingly.

Directive 92/27/EC[25] was later revised by Directive 2001/83/EC[39] in 2001 which dealt mainly with discrepancies between certain national rulings, especially those regarding medicinal products, and attempted to assemble them in a single text in order to safeguard public health within the member states of the European Community. The information that inclusion of package leaflets was obligatory was moved from Article 6 in Directive 92/27/EC to Article 58 in the new directive. Article 59 of Directive 2001/83/EC[39] stated that the '*package leaflet shall be drawn up in accordance with the summary of product characteristics*' and then provided a list of the content and order. Article 63 (2) included the following ruling '*The package leaflet must be written and designed to be clear and understandable, enabling the users to act appropriately, when necessary with the help of health professionals. The package*

leaflet must be clearly legible in the official language or languages of the Member State in which the medicinal product is placed on the market'. Should a package leaflet not conform to the requirements of Directive 2001/83/EC, market authorisation may be refused.

Directive 2004/27/EC[24] subsequently amended Directive 2001/83/EC[39], which resulted in several changes being introduced influencing the order of the contents of the package leaflet. The status of the package leaflet also changed following implementation of Directive 2004/27/EC[24] that made user testing a must for all package leaflets, which studies have shown to be beneficial in ensuring that leaflets are patient orientated[40]. Article 59 (3) thus included the following statement '*the package leaflet shall reflect the results of consultations with target patient groups to ensure that it is legible, clear and easy to use'* while Article 61 (1) declared regarding the package leaflet that '*The results of assessments carried out in cooperation with target patient groups shall also be provided to the competent authority*'.

The latest changes to the package leaflet within the European Union were caused by implementation of new European pharmacovigilance legislation which became applicable in July 2012. Regulation (EU) No. 1235/2010[41] and Directive 2010/84/EU[42], are intended to improve patient safety and health by encouraging patients to directly report adverse drug reactions to the relevant national authorities. Introduction of a black symbol at the start of the package leaflet defined in the Implementing Regulation (EU) No. 198/2013[43] was also intended to show patients whether the medicinal product described in the package leaflet is subject to additional monitoring.

With the intention of harmonising the structure and content of patient information in the Europe Union and connected countries (Norway, Liechtenstein and Iceland), the Working Group on the Quality Review of Documents (QRD) was established in June 1996 by the European Medicines Agency (EMA)[44] who published the first edition of the QRD template in the same year. The QRD template, which is based on Article 65 of Directive 2001/83/EU[39], covers general requirements for the summary of product characteristics, labelling of the product and the package leaflet of medicines. Thirteen updates followed since the first edition of the template for medicines approved via the centralised procedure up to the latest version 9 in March 2013. The QRD template itself is a text framework which provides headings for paragraphs and sub-paragraphs including standard statements applicable for the broad range of distributed medicines. Medicine specific information is inserted into this text frame by the pharmaceutical companies. The QRD template for centralised procedures is available in the 23 official EU languages with the addition of Icelandic and Norwegian and aims to support the pharmaceutical industry in providing user friendly product information. Centralised procedures came into operation in 1995[45] allowing applicants to obtain a marketing authorisation that is valid throughout the EU, Norway, Liechtenstein and Iceland. A slightly

modified version of the QRD template for centrally approved medicines is available for package leaflets approved within mutual recognition (MR) and decentralised procedures (DC)[46]. More extensive templates are also provided for certain product groups such as radiopharmaceuticals[47]. Using the QRD template has the advantage that patients find identical standardised headings and general texts, including the same order of information in package leaflets in each European Union member state plus the three above mentioned associated countries[44].

According to the 'Consolidated versions of the treaty on European Union and of the treaty establishing the European community', article 249, the QRD template is also only a guidance document and therefore not legally required to be implemented into practice[37]. However, the QRD template states on the first page of the annotated QRD template version 9[48] that standard statements given in the template '*...must be used whenever they are applicable*.' Deviation is possible in certain cases to accommodate specific medicinal product needs and will be considered on a case-by-case basis[46]. Although the revised Readability Guideline from 2009 contains no model template, Marketing Authorisation Holders are told to use the QRD templates provided by the EMA. Newer versions of the QRD template use a bracketing convention and different colour text for certain information: curly brackets define information which must be filled in, pointed brackets are for text which can be selected or deleted as appropriate, and text which is not contained in brackets must be used. Throughout the document orange coloured text is used to cross-refer to sections of the SmPC and green text is used for explanations.

During development of QRD template version 8 (for centralised approved medicines) and version 2 (for medicines authorised by other procedures) in 2011, headings and mandatory texts underwent major changes based on information gained from user testing and feedback from various sources, such as agencies, the pharmaceutical industry and academia as well as patient and consumer groups[49]. The above mentioned user testing results are a collection of reported specific problems identified in the previous QRD template version 7.3.1, although the methods used and the data generated which were analysed to come to these conclusions remain unpublished. The most recent QRD template version 9 provided several further text additions as a result of the latest pharmacovigilance legislation[41,42,50]. Despite these significant extensive changes applicable for all package leaflets in the European Union, relevant studies have not been carried out. Furthermore, since the first QRD template was published in 1996, its volume has expanded[48,51]. However, the effect of this increased volume of QRD template text has not been addressed although previous studies have shown the advantages of a short model template of around 200 words, mainly through avoiding repetitions and long sentences[52,53]. Moreover, use of the QRD template is one main reason for increasing package leaflets' text volume with the negative outcome of reduced locatability

of provided information, decreased motivation to read the package leaflets and increased mistrust in using required medicines after reading the patient information[54,55].

2. Objectives

A main focus of the project is whether the extensive changes published in the QRD template version 8[56] provide advantages in readability and understanding for the patient. Therefore, the following main points regarding the QRD template were addressed in detail:

1. Development and implementation of the QRD template:
    - How has the QRD template developed from its initial form to the present day?
    - How are QRD template headings and text elements used in general?
    - How are specific aspects and text blocks implemented?

2. The use of templates for the package leaflet in European and non-European countries:
    - Which templates in German or English exist for the package leaflet in European and non-European countries?
    - Which legal requirements influence the content and structure of package leaflet templates?
    - How do the templates compare to each other in terms of structure and content?

3. Readability test of the QRD template 8, its predecessor and a model version:
    - How is the locatability and comprehensibility of the template texts?
    - How does the template influence the locatability and comprehensibility of medical specific information?
    - Are patients satisfied with the template information provided or where do they see room for improvement?

3. Materials and methods

3.1 Analysis of QRD template development up to the present day

QRD template versions 1 to 7.3.1 in English were kindly provided by the EMA, while versions 8 and 9 were downloaded from the EMA website[46,48,51]. The QRD templates for radiopharmaceuticals[57] as well as that included in the first Readability Guideline published 1998 were also included in the analysis[36].

The black QRD template text in English for package leaflets of centralised approved over-the-counter (OTC) medicines was analysed regarding the number of words using the word count tool from Microsoft Office Word 2007. The bracketing convention in the template whereby information in pointed brackets can be optionally selected or deleted allows for large amounts of black text to be omitted. Therefore, for the minimum possible word count, all optional information was deleted including storage conditions proposed for the package leaflet in section 5. The maximum word count adopted the opposite principle and counted the number of words when all QRD template texts printed in black are counted. The list of the 29 local representatives was not considered in the analysis of the maximum word count. In cases where '<take> <use>' or similar options were provided, only one word of both possibilities was counted, as only one term should be used in the package leaflet.

In addition, the number of long sentences, repetitions and abbreviations used in the black QRD template text was calculated. According to the Readability Guideline of 1998, a sentence was assessed as a 'long sentence' if it contained more than 20 words[36].

Furthermore, the information in black QRD template text of each section was analysed to illustrate the QRD template changes and development up to the current date. The orange text for cross references to the SmPC in the QRD template or the green text used for explanations were not taken into account in this investigation.

3.2 The use of templates for the package leaflet in EU and non-EU countries

One component of the project was to analyse package leaflet templates from different countries, and to investigate the structure and content of these templates. An internet search was initiated to identify the relevant authorities responsible for granting marketing authorisations for pharmaceutical products in English and German speaking countries. The following main criteria were used for the information selection:

- Inclusion of EU and non-EU countries where templates were used for the package leaflet;
- Templates which were available in German or English;
- Search for legal requirements influencing the content and order of the templates in the selected countries;

- Search for national guidelines providing recommendations for the design and content of the package leaflets;
- Search for the history behind the development of templates.

Information in the form of links to guidelines or directives provided on the internet pages of the country specific authorities as well as internet research was used to analyse the history, regulations, content and structure of existing package leaflets and templates. Available templates from each country were then compared to the QRD templates 8/9 in terms of the sections contained, headings used and compulsory statements. Subsequently, templates from the selected counties were compared to each other.

3.3 Analysis of QRD template implementation in package leaflets of centralised approved medicines

All package leaflets in the English language for medicines granted a centralised authorisation and available on the EMA website[58] at a defined date were downloaded and used to analyse how the QRD template is implemented in practice. Medicines which were withdrawn post-approval, suspended or refused were not used in the study. This was repeated twice with a time gap of one year between each download.

For the second and third downloads, only package leaflets which were present in the first download and had been updated were extracted. The data for the unchanged package leaflets were however also integrated into the dataset for analysis in the second and third downloads to investigate how rapidly and to what extent the QRD template had been implemented within the past year.

The package leaflets from each download in the form of PDF files were subsequently converted into Microsoft Office Word 2007 documents for further analysis using the software Adobe Acrobat 9 Standard. The following catalogue of criteria was used to assess each package leaflet and information was coded and analysed using a Pivot table in Microsoft Excel 2007:

- Type of product: pharmaceutical form described in the package leaflet, prescription status, ATC code and grouping by considering the first letter of this code.
- Number of package leaflet words using the tool 'Word count' of the Microsoft Office Word 2007 program: This total word count comprised all information contained in the package leaflet including any additional information present after section 6 of the package leaflet. In addition, leaflets were noted which contained special use instructions for patients, or extra information for health professionals at the end of the leaflet after section 6, and the number of words this information

contained, was counted to allow further analysis of the contribution to the total amount of text that this information is responsible for.

- Number of QRD template words using the tool 'Word count' of the Microsoft Office Word 2007 program: All information was deleted from the package leaflet which was not recognised to be from the black printed QRD template text to measure the volume of text arising from the QRD template. The name of the medicine at the top of the leaflet, and where it was used to replace 'X' in template texts, was also not removed.
- QRD template version: This was determined by examining the wording contained in the contents list, information box and side effects section which differs between template versions.
- Presence of the contents list
- Presence of the black symbol from QRD template 9
- Information contained at the start of the leaflet: Since implementation of QRD template 7[51], four points containing one to three sentences are potentially present in the information box. For each leaflet it was noted which of the following four points were present:
  - 'Keep this leaflet. You may need to read it again'
  - 'If you have any questions ask your <doctor> < or > <pharmacist> (additionally <or nurse>.' in QRD templates 8[49] and 9[48]). A subanalysis was also carried out as to whether only doctor was mentioned, doctor and pharmacist and/or nurse or combinations of other terms.
  - 'This medicine has been prescribed for you (additionally 'only' in QRD templates 8[49] and 9[48]). Do not pass it on to others. It may harm them, even if their symptoms are the same as yours' (prescription only medicines) or 'You must contact a doctor if your symptoms worsen or do not improve' (non prescription medicines) (QRD template 7[51]); Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours (prescription only medicines) or 'You must talk to a doctor if you do not feel better or if you feel worse <after {number of} days> (non prescription medicines) (QRD templates 8[49] and 9[48]).
  - 'If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.'(QRD template 7[51]); 'If you get any side effects, talk to your <doctor> <,> <or> <pharmacist> <or nurse>. This includes any possible side effects not listed in this leaflet' (QRD templates 8[49] and 9[48]). The prescence of sentence 'See section 4' from QRD template 9[48] was also noted.

- Reference to location of list of excipients: In section 2 of the package leaflet, the patient is told not to take the medicine if they are 'allergic (hypersensitive)' in QRD template 7[51] and just 'allergic' in QRD templates 8[49] and 9[48] to the active ingredient or any of the excipients. The package leaflets were examined to see whether the patient was provided guidance in the contraindication section on where to find this information within the leaflet.
- The method of presenting side effects: Whether a table to describe the frequency classes was present at the start of section 4, or if the frequency was described as part of the side effect list was noted. The description type of frequencies was also coded. The use of MedDRA SOCs and whether the most serious side effects were located at the start of the section were additionally assessed.
- List of Marketing Authorisation Holders' representatives: The presence or absence of the list was noted. The number of words in this list was determined again using the word count tool from Microsoft Office Word 2007. Furthermore, which information was present in this list was recorded: MAH representative name, post address, telephone number, email address.
- Subanalysis relating to template wording use: To examine how widely headings and standard statements from QRD templates 7 and 8/9 were used in package leaflets, an additional subanalysis involving aspects of the templates which differ between QRD templates 7 and 8/9 was undertaken. A yes or no decision was made as to whether the elements of either template 7 or 8/9 shown in table 1 were present in the examined leaflets.

As it was not possible to convert all downloaded package leaflets into word documents in the first download, it was analysed whether the investigated group of package leaflets was representative of the total sample which were available for centralised approved procedures on the EMA website. The analysed package leaflets were therefore analysed to the total sample group with respect to:

- sales status: prescription only or OTC
- indication as defined by the first letter of the ATC code
- pharmaceutical form

The pharmaceutical forms were divided into 5 main groups: film-coated tablets, parenteral administration forms (injections and infusions), all other tablets (including dispersible, buccal, prolonged release), all capsules (including soft, hard, gastro-resistant) and others (nasal spray, eye drops, transdermal plasters, gases). Then the percentage of the products which fell into each of the three categories described above was determined for the group of analysed package leaflets and the package leaflets of the complete sample set on the EMA website. Subsequently, the upper and lower limits of the 95 % confidence interval for the percentage of examined package leaflets was calculated using the following formula:

Upper limit: $g_u = (rh(A) + u_{1-\alpha/2} \times (rh(A) \times (1 - rh(A)) / n)^{1/2}$

Lower limit: $g_u = (rh(A) - u_{1-\alpha/2} \times (rh(A) \times (1 - rh(A)) / n)^{1/2}$

rh(A) = relative frequency of an observed parameter from the total sum

α = 1 – observed confidence interval (for the 95 % confidence interval $\alpha = 1 - 0.05 = 0.05$)

$u_{1-\alpha/2}$ = Quantile of the normal distribution (for the 95 % confidence interval $u_{0,975} = 1.96$)

n = total number

Table 1: Elements contained in QRD templates 7 and 8/9

Template heading/standard text	**QRD template 7[51]**	**QRD templates 8[49]/9[48]**
Contraindication sentence in section 2 under 'Do not <take> <use> X:	if you are allergic (hypersensitive) to ….	if you are allergic to…
Warnings and precautions subheading	Take special care with X	Warnings and precautions
Standard statement regarding interactions with other medicines	Please tell your <doctor> <or> <pharmacist> if you are <taking> <using> or have recently <taken> <used> any other medicines, including medicines obtained without a prescription.	<Tell your <doctor> <or> <pharmacist> if you are <taking > <using>, have recently <taken> <used> or might <take> <use> any other medicines.
Subheading for interactions with food and drink	<Taking> <Using> X with food and drink	X with <food> <and> <,> <drink> <and> <alcohol>
Subheading regarding pregnancy, breast-feeding, fertility	Pregnancy and breast-feeding	Pregnancy <and> <,> breast-feeding <and fertility>
Optional statement for pregnant or breast-feeding women	<Ask your <doctor> <or> <pharmacist> for advice before taking any medicine>	<If you are pregnant or breast-feeding, think you might be pregnant or are planning to have a baby, ask your <doctor> <or> <pharmacist> for advice before taking this medicine>
Excipients warnings subheading	Important information about some of the ingredients of X	X contains {name the excipient(s)}

Template heading/standard text	**QRD template 7[51]**	**QRD templates 8[49]/9[48]**
Side effect warning sentence at the end of section 4	If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your <doctor> <or > <pharmacist>	*Template 8:* If you get any side effects, talk to your <doctor> <or> <,>pharmacist> <nurse>. This includes any possible side effects not listed in this leaflet *Template 9:* **Reporting of side effects** If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

3.3 Readability test of the QRD template version 8, its predecessor and a model version

3.3.1 Development of package leaflets in three different templates

To achieve the aims set out in chapter 2, package leaflets were developed using the QRD template for centralised approved medicines version 7.3.1 or 8 or a model template with around 200 words[52] which had been tested in a previous study and is based on the QRD template. The QRD template for centralised procedures was chosen to enable inclusion of the 29 optional representative addresses of the marketing authorisation holders. Each leaflet was printed with an identical layout and design to enable comparison between template versions and ensure standardised conditions. The maximum text version was used for both QRD templates according to the bracketing convention. The BfArM sample text for the prescription only ACE-inhibitor enalapril[59], which was publicly available at the start of the project and had been used in previous studies[52,53], was chosen to fill in the text frameworks (appendix 1). Versions of the leaflet were created in German which contained the full length of the sample text provided by BfArM using the three templates (see appendices 2, 3, and 4 for long German package leaflets). This text was then shortened and optimised - named in this work as short text throughout - to contain identical information but as a series of concise bullet points in the same templates, to provide an easily readable and comprehensive text (see appendices 5, 6 and 7). This method ensured comparability to similar texts with a model template tested in a previous study which had been improved in terms of comprehensibility[53]. These three short leaflets were then translated into English (see appendices 8, 9 and 10). Three groups of package leaflets were thereby the result; long and short text versions with the three templates for testing in Germany, and a short text version for use in England. The template text varied in each package leaflet group whereas the package leaflet text always remained the same.

In the interaction section contained in package leaflet section 2, colons were used in the English and German short version of the leaflets with the model template and QRD 7.3.1 to separate the name of the active ingredient - which may interact with enalapril - and the patient friendly explanation. In leaflets with template version 8, the name of the active ingredient was listed first and the patient friendly explanation was enclosed in brackets according to the recommendations of this template version.

Different methods for the description of the frequencies of side effects were used according to the template versions: a table at the beginning of the provided side effects was used in leaflets with QRD template version 7.3.1, and an explanation at the beginning of each side effect group in that using the model template and QRD template version 8. In leaflets with version 8, side effects were divided into serious and other - this was not the case in the other template versions. The model template accentuated serious side effects in bold and did not include an extra paragraph for countermeasures in the case of serious side effects in section 4 as this information was integrated into the list of side effects.

In section 6 of the shortened text versions of both languages, ‘other ingredients’ were listed alphabetically rather than according to the amount contained in the described enalapril tablets, and E-numbers and the abbreviation Ph.Eur nomenclature were not included. Leaflets with QRD templates 7.3.1 and 8 contained the list of 29 representatives of the MAH holder in section 6.

A slight difference exists in QRD template version 8 in section 2 between translations whereby the cross-reference to other ingredients in section 6 is given in brackets in the English QRD template version, but not in the German one, where it is included in the running text.

During the preparation phase, leaflets were carefully edited for spelling and grammatical errors and checked that they were compliant to the relevant template. The word texts were then type-set into a mock-up format using Adobe InDesign CS4 software. This program allowed the files to be converted into PDFs for printing in a typical form which is used for package leaflets that are readability tested and subsequently distributed on the market. To avoid errors, the Schlafender Hase Text verification Tool 5.1.1 was used to compare the prepared PDF documents with the original Word texts. Identical type size, paper, layout and design were used in each package leaflet and questionnaire in both countries.

3.3.2 Development of the questionnaire

A written readability test questionnaire was developed based on those which had been used and tested in previous studies[52,53]. The questionnaire contained an introductory letter followed by sections for:

a) demographic data
b) rendition of the package leaflet’s contents
c) participant’s personal opinion on the leaflet.

Demographic data which was to be filled in by the participants after receiving the questionnaire included age, level of education, postcode, reading habits and the number of medicines taken at the time of the study for each participant.

The second part of the questionnaire for ‘rendition of the package leaflet’s content’ assessed using the written readability test, whether participants could find certain information contained in the package leaflet and know how to act on it. The 26 questions in this section were worded to test key template text messages rather than knowledge on the active ingredient of the medicine itself. Care was taken with the formulation of the questions by using other wording than that contained in the package leaflet to avoid

information being found simply by word comparisons. At least one question was included relating to each testable template section heading or standard template sentence in the package leaflet. As the recommendations in the green explanatory text in the template were also to be tested, for example, the suggested method of describing side effect frequencies was tested for comprehensibility. More than one question was present for key safety messages such as how to act when side effects occur. Considerably less content related questions than in this study are usually used in a readability test where according to the Readability Guideline[38], 12 - 15 questions are sufficient, although this is based on a test involving an interviewer. A conscious decision was made to include more questions than recommended, as the test described in this study did not involve an oral interview and was designed to test the template text meaning sufficient questions were required to test all sections (personal communication, Dr. J. Fuchs). No time limit was set in which this section had to be completed, but participants were instructed to note the time when they started answering the content questions, and then again when they had finished. The time taken to answer each individual question was not measured.

Three categories were used for analysis of the data relating to the content questions:

1. Correct answer
2. Wrong answer
3. Answer not found (if an answer was not found, a box was provided which could be ticked by the participants)

The third part measured personal opinions to 15 statements regarding readability, length of information, comprehensibility, layout and confidence in the medicine which were intended for assessment by participants using a five point Likert scale shown in the right column of table 2. This scale has previously been used and found to be acceptable[60]. In an extra section at the end of the questionnaire, participants were then asked to describe in free text their opinion on the read package leaflet, and what, if anything should be added or deleted. The questionnaires can be seen with the correct answers in appendices 11 and 12. The English questionnaire was a faithful translation of the German version.

Before the first readability test round was carried out, a pilot test was performed with the prepared leaflets and questionnaires to ensure that they worked in the practice, even though this is not compulsory for the written readability test method[61]. In this pilot test, two people read each version of the short package leaflet in England and Germany, and four people read the long BfArM text versions of the leaflet in Germany. As the questionnaires and short package leaflets are direct translations of each other, four people had therefore read each short version of the leaflet, and four people the long BfArM text version in each of the three templates. The order in which each of the three package leaflets in a group was read, was

random. An approximately 10 day time interval was maintained between reading each package leaflet and participants subsequently filled in the questionnaire. A 10 day time interval was chosen to rapidly gain feedback as to whether the questionnaire was suited to testing the package leaflets. The answers provided were subsequently analysed to see if either the printed layout of the package leaflet in terms of changing line-breaks or positioning of sections, or the questions contained in the questionnaire needed any alterations as they led to misunderstandings. For example, finding information for a certain side effect involving the liver was found inappropriate as liver-related problems were also contained in other sections of the package leaflet.

3.3.3 Study execution

Readability testing is the current gold standard used within the European Union to evaluate package leaflets. The written readability test method, also known as the 'self-completion method', which is widely accepted within the European Union[61], was considered to investigate the locatability and comprehensibility of the template texts. The readability test was carried out using a cross-over study design whereby each subject had to read all three versions of the leaflet and answer the questionnaire described in section 3.3.2. A 6 month time interval was applied between testing each template version of the leaflet as this is an officially recommended time gap between two readability tests carried out with one person[62]. To obtain robust data, it was decided to recruit over 60 participants per package leaflet group as this is three times the recommended number for a readability test[38]. The participants were given the questionnaire with identical questions in each of the three test rounds per package leaflet group, whereby in each test round the template varied while the medical specific package leaflet text remained the same.

The selected participants should be representative of everyone who might take a medicine and therefore during recruiting, participants with a broad range of literacy and age were included as long as they were considered to be able to independently read the leaflet and answer the questionnaire. Subjects from the medical profession were excluded from the study. As it is possible that medications are taken independently by teenagers, they were also included in this study, an additional advantage being that they are not the target group for enalapril and therefore probably have no previous knowledge of either the medicine or the indication.

Recruiting of participants was predominantly in the Lichtenfels and Bamberg areas in Germany to test the German versions of the package leaflets, and in the Cambridge area in England for the English versions. Subjects were selected randomly and participation was voluntary. Before handing out the package leaflets and questionnaires, the purpose of the test was explained to the participants, who were also shown the explanatory notes in the cover letter and instructions at the beginning of the questionnaire. Participants

were reassured that neither their memory nor intelligence was being tested and that the leaflet could be referred to during the answering of the questionnaire.

3.3.4 Statistical analysis

All answers provided in the returned questionnaires for each of the three rounds of the readability test were coded and entered into an SPSS 15.0 table. Double data entry was carried out to avoid input data errors. For the demographic data, the average age of the participants involved was calculated as well as the average number of years at university for those subjects who had been university educated. Minimum and maximum time in hours that participants spent reading a day, and how long participants occupied themselves with medical reports a week were also noted.

The calculated medians in percent of the total number of correctly and incorrectly answered questions, as well as where the information was not found were calculated for each leaflet version. For each individual question, the percentages of correct and incorrect answers, as well as where the information was not found for a particular question were calculated for each leaflet and template version. The calculated median was used again to determine the time needed to answer the questions for 'rendition of the package leaflet's contents' in order again to avoid negative influences of outliers and extreme values in the analysis.
Significant statistical differences between the three template versions regarding total correct, wrong and not found answers and locatability time per template in each leaflet group were calculated using the global non-parametric Friedman test in SPSS followed by the non-parametric Wilcoxon test between paired samples[63]. Subsequently the Holm-alpha correction method was used[64].

It was then investigated whether the template used had influenced whether a question had been answered correctly or not. Statistically significant differences between the results for each individual content question between template versions in a group were calculated using the Cochran test as a global test followed by the McNemar test which compares two single values, and subsequently the Holm-alpha correction method was used according to Schaffer[64]. Any significant influence of demographic factors was examined using Pearson's chi-square test in the SPSS program followed by the Holm-alpha correction method according to Schaffer[64].

Before analysis of participants' opinions regarding comprehensibility, layout and legibility of the package leaflet, the answers to 6 of the 15 questions were recoded, as the original question had been worded to avoid participants simply answering every question with 'yes'. Following recoding, the calculated medians were determined for each question (table 2).

Table 2: Range for assessment criteria for participants' opinions on the package leaflet

Range	Participants' opinion
1.00 to 1.50	Yes
1.51 to 2.50	Mostly yes
2.51 to 3.50	Other
3.51 to 4.50	Mostly no
4.51 to 5.00	Not at all

To detect significant differences between the personal opinions about the package leaflet for each template version used, the non-parametric Sign test for 2 related samples in SPSS was used followed by the Holm-alpha correction method according to Schaffer[64]. Thus, the personal responses regarding each package leaflet for each question were compared to each other in pairs.

For the four free text questions contained at the end of the questionnaire, the responses provided by the participants were coded and entered into SPSS. The frequency with which a particular response occurred for each package leaflet was counted.

4. Results

4.1 QRD template development up to the present day

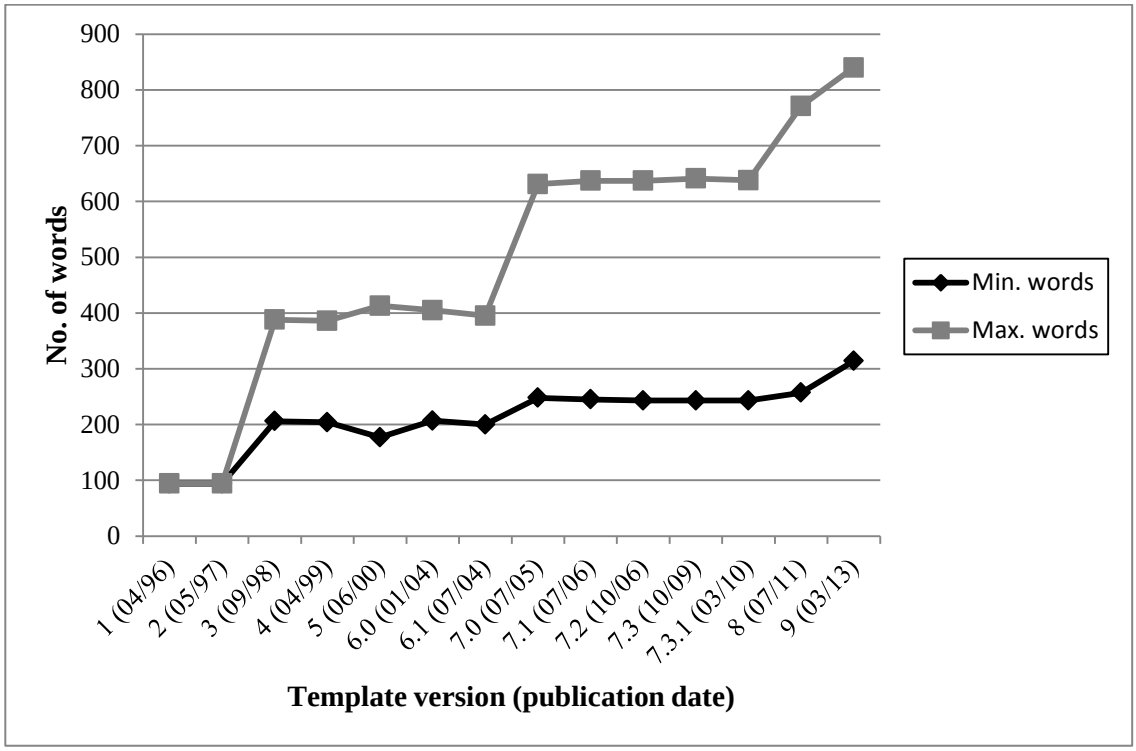
4.1.1 Number of QRD template words for package leaflets of OTC medicines

The first two published versions of the QRD template for OTC medicines included only twelve section headings which literally reflected the information required by article 7 of Directive 92/27/EEC which was in force at that time[25]. No general advice or subheadings were provided that should be used verbatim in package leaflets, therefore the number of words used in both template versions was only 94 (shown in the figure). Although the QRD template version 3 was based on the same directive as both its predecessors, it had already taken on a form similar to that which we recognise today using mandatory main headings and subheadings plus general informative phrases. In version 3, the number of main section headings was reduced to five, the placeholder 'X' was used in the template to fill in the name of the medicine, pointed brackets were used for optional texts and explanations were given in green ink. These changes caused the number of words to increase greatly as seen in the figure and reflected the package leaflet example of the first Readability Guideline which was also published in September 1998, as was QRD template version 3[36]. The increase in the maximum number of words was plainly greater than the minimum number of words as shown in the figure, a situation which applies up to the QRD template version 9[48] published in March 2013. Although the template for radiopharmaceuticals[57] cannot be directly compared to those described as it is for prescription only medicines, it was of interest to see that it contains by far the most words, the minimum being 762 and the maximum 1154.

QRD template versions 4 to 6.1 were published between August 1999 and July 2004. Template version 6 was the earliest to include information in the package leaflet as required by Directive 2001/83/EC[39]. In version 6.1, orange text was used for the first time to cross-refer to sections in the SmPC which should be reflected in that particular section in the package leaflet. The QRD template version 7.0 was published in 5 different editions between 2005 and 2010 and was the earliest to be available as an annotated and non-annotated edition on the EMA website. In the advisory text at the start of QRD template version 7.0 (published July 2005) it was stated that applicants had to make sure that the package leaflet was made available in formats appropriate for the blind and partially sighted, reflecting Article 56 (a) of Directive 2004/27/EC[24]. Furthermore, the new order of information published in this directive was considered, for example, all ingredients had to be listed in the final section of the package leaflet instead of at the beginning. QRD template version 8 (published in July 2011) shows many changes in the package leaflet when compared to its predecessor 7.3.1[65]. Detailed explanations are given in green text in all sections and cross references to the relevant sections in the SmPC are provided in orange. Many more subheadings are present such as regarding use by children and adolescents reflecting changes which were previously made to the SmPC in QRD template version 7.3.1. This is stated in QRD template version 8 to be an attempt to

make it easier for patients to navigate their way through the package leaflet. Pointed brackets are used more frequently in version 8 meaning that more standard statements are optional than in previous templates which could result in a reduction in the minimum number of template words required for package leaflets, but the figure shows the outcome to be the opposite.

Figure: Number of words in the QRD template intended for OTC products



In March 2013, a new QRD template (version 9)[48] was published which offered an amendment for medicinal products which are subject to additional monitoring. This in the form of a black inverted triangle, and an appropriate related explanatory text. The information box at the start of the package leaflet should also include a cross-reference to section 4 to aid the user in locating possible side effects. Two standard sentences in section 4 further encourage users to report any adverse reactions. These new text passages were due to the implementation of the pharmacovigilance legislation[42]. Template version 9 again increased the number of words contained in the QRD template.

4.1.2 Repetitions, long sentences and abbreviations in the QRD template

Avoid long sentences of over 20 words in length and abbreviations are two recommendations of the first Readability Guideline of 1998[36]. Repetitions should also be eliminated as this leads to an increase in the volume of text. All versions of the template - except 1 and 2 - use sentences of over 20 words and recurring information. While versions 3 to 6.0 only used one repetition of the same content, this number

increased to two in version 6.1, three repetitions in versions 7.0 to 7.3.1 and four since version 8. A similar trend was seen in the number of long sentences, with two sentences of over 20 words in QRD template versions 3 to 6.1 and three in versions 7.0 to 7.3.1. However, versions 8 and 9 showed an improvement with only one long QRD template sentence.
Abbreviations are only found at the end of the package leaflet in version 7.0, with 'EMEA' and from version 8 'EU/EEA' (European Union/European Economic Area).

4.2 Development of the QRD template wording

This following section demonstrates the development of the QRD template wording from its first version up to version 9 of March 2013.

4.2.1 QRD template section headings

All versions of the QRD template except versions 1 and 2 start with a contents list. The annotated QRD template version 8 states that user testing has shown that an index is valued by patients, although user testing research illustrates that package leaflets without one are not at a disadvantage[49,52,53].
In the Readability Guideline template and QRD template versions 3 to 9, the headings of sections 1, 3 and 4 use the same wording. In version 5, section 6 was included for using the heading 'Further information'. The heading of section 2 was altered in version 8 into 'What you need to know before you <take> <use> X' and that of section 6 into 'Contents of the pack and further information', to provide the reader with more details about the content to be expected in both sections (table 3).

Table 3: Development of template main section headings to be used in package leaflets

<table>
<tr><th>Template version</th><th>Section 1</th><th>Section 2</th><th>Section 3</th><th>Section 4</th><th>Section 5</th><th>Section 6</th></tr>
<tr><td>Readability Guideline[36], QRD template 3 - 4[51]</td><td rowspan="4">What X is and what it is used for</td><td rowspan="2">Before you <take> <use> X</td><td rowspan="4">How to <take> <use> X</td><td rowspan="4">Possible side effects</td><td rowspan="2">Storing X</td><td>-</td></tr>
<tr><td>QRD template 5 - 6.1[51]</td><td rowspan="2">Further information</td></tr>
<tr><td>QRD template 7.0 - 7.3.1[51]</td><td rowspan="2">How to store X</td></tr>
<tr><td>QRD template 8[49] and 9[48]</td><td>What you need to know before you <take> <use> X</td><td>Contents of the pack and further information</td></tr>
</table>

4.2.2 The information box

The first two versions of the QRD template provided no information box or index for the beginning of package leaflets, but began with all active substances and excipients after the name of the medicine. From version 3, an information box was present at the start of the package leaflet template which distinguished between prescription only (Rx) and medicines available without prescription. The bracketing convention means that the information can be adapted to the product requirements i.e. to reflect whether the medicine is only administered by a doctor or bought by the patient. Strictly speaking, the brackets could also be interpreted to mean that the entire box is optional which would cause a reduction of around one hundred template words. The wording in the information box is the same in versions 3 to 6.1. Following some changes, versions 7.0 to 7.3.1 were also identical. However, differences are seen in the information box depending on whether a product is OTC or Rx. From version 8, a user who has been prescribed a medicine is told to ask a doctor, pharmacist or nurse for more information, whereas the consumer of an OTC preparation is only told to consult a pharmacist. The user of a prescription medicine is also told not pass it on to others which is not required for OTC medicines. From version 8, the MAH is actively instructed not to include this sentence for Rx products only used in a hospital setting. If an OTC product has been bought the consumer is advised to consult a doctor if the condition does not improve after a certain number of days.

Version 9 from 2013 includes a cross-reference to section 4 for the location of side effects although such a cross reference to section 4 has been shown in results from readability testing not to be necessary[66].
Version 9 also introduces for the first time a black symbol (a black inverted equilateral triangle) for medicinal products subject to additional monitoring for reasons of their specific safety profile which includes new active substances, biological medicinal products, medicines given conditional approval, as well as those listed by the Pharmacovigilance Risk Assessment Committee (PRAC)[43]. This form of this black symbol was described in the Commission Implementing Regulation (EU) No 198/2913[43].
For OTC medicines, the statement that 'This medicine is available without prescription' is omitted from version 8 for reasons which are not defined. The starting sentence and the advice to keep the leaflet are the only sentences of the information box which are not found elsewhere in the QRD template versions 8 and 9. Reasons why these repeats are absolutely necessary are not provided in the advice contained in the template. Table 4 presents the differences between template versions in the texts to be used after the name of the medicine and active substances at the beginning of the package leaflet.

Table 4: Template texts to be used after the name of the medicine and active substances at the beginning of the package leaflets for OTC medicines (changes in comparison to the predecessor are highlighted in grey)

Template version				
Readability. Guideline template*[36], QRD template 3 - 4[51]	**QRD template 5 - 6.1[51]**	**QRD template 7.0 - 7.3.1[51]**	**QRD template 8[49]**	**QRD template 9[48]**
-------			---------	< ▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.>
<Read all of this leaflet carefully because it contains important information for you.			<Read all of this leaflet carefully before you start <taking> <using> this medicine because it contains important information for you.	

<table>
<tr><th colspan="5">Template version</th></tr>
<tr><th>Readability. Guideline template*[36], QRD template 3 - 4[51]</th><th>QRD template 5 - 6.1[51]</th><th>QRD template 7.0 - 7.3.1[51]</th><th>QRD template 8[49]</th><th>QRD template 9[48]</th></tr>
<tr><td>This medicine is available without prescription, for you to treat mild illness without a doctor’s help. Nevertheless you still need to use X carefully to get the best results from it.</td><td>This medicine is available without prescription. Nevertheless you still need to use X carefully to get the best results from it.</td><td>This medicine is available without prescription. However, you still need to <take> <use> X carefully to get the best results from it.</td><td colspan="2">Always <take> <use> this medicine exactly as described in this leaflet or as your <doctor> <,> <or> <pharmacist> <or nurse> <has> <have> told you.</td></tr>
<tr><td colspan="5">Keep this leaflet. You may need to read it again.</td></tr>
<tr><td colspan="5">Ask your pharmacist if you need more information or advice.</td></tr>
<tr><td colspan="2">You must see a doctor if your symptoms worsen or do not improve after {number of} days.></td><td>You must contact a doctor if your symptoms worsen or do not improve <after {number of} days.></td><td>If you get any side effects, talk to your <doctor> <,> <or> <pharmacist> <or nurse>. This includes any possible side effects not listed in this leaflet.</td><td>If you get any side effects, talk to your <doctor> <,> <or> <pharmacist> <or nurse>. This includes any possible side effects not listed in this leaflet. See section 4.</td></tr>
</table>

Template version				
Readability. Guideline template*[36], QRD template 3 - 4[51]	**QRD template 5 - 6.1[51]**	**QRD template 7.0 - 7.3.1[51]**	**QRD template 8[49]**	**QRD template 9[48]**
----------		If any of the side effects gets serious, or if you notice any side effect not listed in this leaflet, please tell your <doctor> <or> <pharmacist>.>	You must talk to a doctor if you do not feel better or if you feel worse <after {number of} days>.>	

*The pointed brackets are not found in the Readability Guideline template but are included in the QRD template versions.

4.2.3 Section 1 of the QRD template

In the Readability Guideline template and QRD template versions 3 to 6.1, the name of the product, active substances, list of excipients, name of the MAH and manufacturer were stated between the list of contents and the start of section 1 of the package leaflet. In template versions 1 and 2, sections 1 to 5 dealt with this information under clearly defined headings. The Readability Guideline from 1998[36] mentions that the European Commission was aware that the leaflet would be more readable if this information was placed towards the end of the leaflet, but due to the order stipulated in the current Directive 92/27/EEC[25] it was included at the predetermined position until the ruling could be modified. In QRD template version 7.0, the aforementioned information was moved to section 6 due to the implementation of Directive 2004/27/EC[24], which altered the order of contents in the package leaflet.

Section 1 in template versions 3 to 7.3.1 has always been used to define the pharmacotherapeutic group and type of activity of the active ingredient. This information is found in section 6 of template 1 and 2. Explanatory text in subsequent versions of the template mentions that the therapeutic indications should be stated in patient understandable language. From QRD template version 8 it is allowed that information on the benefits of using the medicine can be included ‘as long as it is compatible with the SmPC, useful for the patient and not of a promotional nature’[49].

In section 1, the QRD template from versions 3 to 7.3.1 only recommended one black printed sentence which was for optional use only - ‘This medicine is for diagnostic use only.’ This was deleted in version 8

and the following was newly inserted ‘You must talk to a doctor if you do not feel better or if you feel worse <after {number of} days.’ - a verbatim repetition of the last bullet point of the information box used for OTC medicines[49]. This sentence is retained in QRD template 9.

4.2.4 Section 2 of the QRD template

Section 2 is usually the largest in the package leaflet in terms of subheadings, and therefore the use of carefully worded subheadings is crucial to aid the patient in finding relevant information.

Template versions 3 to 9 started with contraindications listed under ‘Do not <take> <use> X’ (table 5)[48,49,51]. The statement under ‘Do not <take> <use> X’ informs patients not to use the medicine if an allergy to one of the ingredients exist. Beginning with the wording ‘hypersensitivity (allergy)’ used in version 3, this text was amended in version 7.0, and corrected from version 8 to ‘if you are allergic to {active substance(s)} or any of the other ingredients of this medicine (listed in section 6)’[48,49,51].

Warnings and precautions are provided under the next section 2 subheading which read up to version 7.3.1 ‘Take special care with X’[51]. This was changed from version 8 to the ‘Warnings and precautions’ subheading followed by the mandatory advice according to the template’s bracketing convention that patients should contact healthcare professionals if listed aspects apply to them[48,49]. Other additions from QRD template version 8 are inclusion of alcohol in the food and drink subheading and the insertion of fertility in the pregnancy and breast-feeding section if facts are known. The amended subheading ‘X contains {name of excipient(s)}’ emphasises any excipients which need to be drawn to the user’s attention[48,49].

Table 5: Subheadings (in bold) and standard statements (normal type) used in section 2 of the template (changes in comparison to the predecessor are highlighted in grey)

<table>
<tr><th colspan="4">Template version</th></tr>
<tr><th>Read-ability Guideline, QRD template 3 - 6[51]</th><th>QRD template 6.1[51]</th><th>QRD template 7.0 - 7.3.1[51]</th><th>QRD template 8[49] and 9[48]</th></tr>
<tr><td colspan="4">Do not <take> <use> X<:></td></tr>
<tr><td colspan="2"><if you are hypersensitive (allergic) to {active substance} or any of the other ingredients of X></td><td><if you are allergic (hypersensitive) to {active substance(s)} or any of the other ingredients of X.></td><td><if you are allergic to {active substance(s)} or any of the other ingredients of this medicine (listed in section 6).></td></tr>
<tr><td colspan="3">Take special care with X</td><td>Warnings and precautions</td></tr>
<tr><td colspan="3"><if you ….></td><td>Talk to your doctor <or> <pharmacist> <or nurse> before <taking> <using> X</td></tr>
<tr><td colspan="3"></td><td>Children and <adolescents></td></tr>
<tr><td></td><td colspan="2"><Taking> <Using> other medicines</td><td>Other medicines and X</td></tr>
<tr><td colspan="2"></td><td><Please tell your <doctor> <or> <pharmacist> if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.></td><td><Tell your <doctor> <or> <pharmacist> if you are <taking> <using>, have recently <taken> <used> or might <take> <use> any other medicines.></td></tr>
<tr><td colspan="3"><Taking> <Using> X with food and drink</td><td>X with <food> <and> <,> <drink> <and> <alcohol></td></tr>
<tr><td colspan="2">Pregnancy
Breast-feeding</td><td>Pregnancy and breast-feeding</td><td>Pregnancy <and> <,> breast-feeding <and fertility></td></tr>
<tr><td colspan="3"><Ask your doctor or pharmacist for advice before taking any medicine.></td><td><If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your <doctor> <or> <pharmacist> for advice before taking this medicine.></td></tr>
</table>

Template version			
Read-ability Guideline, QRD template 3 - 6[51]	**QRD template 6.1[51]**	**QRD template 7.0 - 7.3.1[51]**	**QRD template 8[49] and 9[48]**
Driving and using machines			
Important information about some of the ingredients of X			**<X contains {name the excipient(s)}>**
<Taking> <Using> other medicines*			
<Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed>			

*Double use of '<Taking> <Using> other medicines' in version 6.1 is probably a mistake in the template.

4.2.5 Section 3 of the QRD template

In QRD templates 1 and 2, section 8 was designated to contain the 'Instructions for proper use', while from QRD template version 3 onwards and in the Readability Guideline template, package leaflet section 3 is for dosage instructions - advice on dosage, method and duration of use - followed by three subsections relating to administration errors - overdose, missing a dose and stopping treatment[36,48,49,51].
Black printed subheadings have only been present since QRD template version 3 for the three administration error sections. The subheading 'Use in children' has been part of the QRD template since version 7.3.1 and was changed from QRD template version 8 to 'Use in children and adolescents'[48,49,51].
General advice with almost identical wording has been provided in black ink for the start of section 3 since QRD template version 5 which informs patients to always use the medicine as the doctor has instructed and to check with the doctor or pharmacist if they are unsure. From QRD template version 8 slightly different wording is provided to be used in the case of OTC medicines. Moreover, version 8 provides for the first time three black printed sentences for optional use relating to the divisibility of tablets depending on the appearance of the score line.

The number of standard statements has greatly increased from version 3 to version 9. The influence of Council Directive 2004/27/EC[24] is reflected in versions of the template onwards from 7.0, which was

published in 2005. QRD template versions 2 to 6.1 and the Readability Guideline template also included the optional sentence '<If you have the impression that the effect of X is too strong or too weak, talk to your doctor or pharmacist.>' which was deleted from version 7.0 onwards. The extra statement that patients should consult their doctor or pharmacist in the case of further questions results from an addition in Article 59 (d) which regulates the instructions for use of the product. The last sentence in this section now reads 'a specific recommendation to consult the doctor or the pharmacist, as appropriate, for any clarification on the use of the product'.

4.2.6 Section 4 of the QRD template

Section 9 of QRD templates 1 and 2 contained the heading 'Description of undesirable effects under normal use' and Directive 92/27/EEC instructed that the actions to be taken must be explained if side effects should occur, including the communication of undesirable effects to the doctor or pharmacist, especially if they are not mentioned in the package leaflet[25]. This general advice has been printed in black since QRD template version 3, including a second general sentence to be written at the beginning of package leaflet section 4 that all medicines can cause side effects (table 6).

From QRD template 8, an optional subheading regarding children and adolescents is inserted providing for the fact that additional side effects may occur which only affect this age group are found. It is only since QRD template 8 that the patient has been advised to contact healthcare professionals if any side effects occur. Previous template versions recommended that patients should contact an expert if the side effect gets serious or is not listed in the package leaflet. This caused patients to understand that they should not contact healthcare professionals in the case of a side effect which is listed in the package leaflet[53].

QRD template 9 includes the new subheading 'Reporting of side effects', followed by a mandatory text where the patient is actively encouraged to report any symptoms to different national contacts, when they are believed to be side effects of using the medicine. This was brought about by the new pharmacovigilance directives[41,42]. Several examples of wording are provided by the template in the green printed explanatory text and an additional Annex V gives the names and addresses of the national authorities where side effects should be reported directly by the patient. This new wording has caused an additional increase in the number of words by over 30 in the English template version.

Table 6: QRD template standard statements intended for use in package leaflet section 4 (changes in comparison to the predecessor are highlighted in grey)

Template version			
Readability Guideline[36], QRD template 3 - 6.1[51]	**QRD template 7.0 - 7.3.1[51]**	**QRD template 8[49]**	**QRD template 9[48]**
Like all medicines, X can have side effects	Like all medicines, X can cause side effects, although not everybody gets them.	Like all medicines, this medicine can cause side effects, although not everybody gets them.	
-	-	<Additional side effects in children <and adolescents>>	
If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.	If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your <doctor> <or> <pharmacist	If you get any side effects, talk to your <doctor> <or> <,> <pharmacist> <or nurse>. This includes any possible side effects not listed in this leaflet.	**Reporting of side effects** If you get any side effects, talk to your <doctor> <or> <,> <pharmacist> <or nurse>. This includes any possible side effects not listed in this leaflet. You can also report any side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

Apart from the changes in the black QRD template text, the green explanations which were provided in this section in the annotated QRD template version 8, noted that serious side effects should be listed first together with the most frequently occurring side effects. Clear handling instructions for the patient should also be given in the case that serious side effects should occur. This should be followed by a list of other side effects arranged according to descending frequencies. This method reflects advice contained in the Readability Guideline[36]. The green explanatory text in template version 9 was however changed to provide the advice that the most serious side effects should be listed first followed by ‘a list of all other side

effects, listed by frequency and starting with the most frequent (without repeating the most serious and most frequent included above)'[48]. A frequency convention for side effects has also been recommended since QRD template 8 (annotated version), where MedDRA system organ classes (SOC) should not be used as the latter uses terms unfamiliar to patients[38,67].

4.2.7 Sections 5 and 6 of the QRD template

In the first two QRD templates, section 10 was designated for reference to the expiry date, storage precautions and visible signs of deterioration. Since QRD template version 3 was developed, section 5 was to be used for this storage information and instruction on keeping the medicine out of sight and reach of children. Wording differs only very slightly between the Readability Guideline template and QRD template versions 3 to 5. The advice to store medicines away from children was omitted in versions 6.0 and 6.1 for unnamed reasons and information relating to disposal of no longer required medicines has been part of the QRD template since version 7.0. The statements contained in section 5 have undergone slight changes mainly of an editorial nature since they were initially published. Standard storage statements were originally included in the QRD template until version 6.0 when these were put into an appendix.

Section 6 was originally not included in versions 3 to 5 of the QRD template as the information which is now presented here had to be provided during the currency of these versions before the indication section according to Directive 92/27/EEC[25]. Versions 6.0 and 6.1 provided in the sixth section a list of local MAH representatives and information relating to the last approval of the package leaflet. Up to date, this list has always been optional but where one MAH representative address is presented, the addresses of all EU/EEA countries must be included according QRD template versions 7.0 to 9.

The change in the information provided in section 6 caused by Directive 2004/27/EC was seen for the first time in QRD template version 7.0[24]. Since this time, information relating to active substances, excipients, description of the product, contents of the pack, the MAH and manufacturer must be provided at the end of the package leaflet. The date of last approval was changed in version 8 to the last revision even though this has been a requirement since Directive 2001/83/EC came into force[39]. After this date, three standard statements were included from QRD template version 7.0 onwards. The first should be used for medicines approved under 'conditional approval' and states that more evidence is to come about the medicine, and the second is for authorisations under 'exceptional circumstances' for example due to the rarity of the disease. The third statement is intended for all centralised approved medicines and notes the EMA website for more detailed information about the medicine. Subsequent to these three statements, information for

healthcare professionals can be presented since QRD template version 5 came into effect, however, this is not compulsory.

4.3 Templates and related legal requirements in selected European and non-European countries

Templates for the package leaflet have been developed within and outside Europe due to relevant national laws which govern the order and content of information, and therefore a thorough analysis of the legal situation in countries where templates are used was considered to be an important stage in the project to provide a comparison of what is considered important for patients by the authorities. On the basis of the criteria described in section 3.2, Germany, the United Kingdom, New Zealand, Australia, Switzerland and the United States were chosen for analysis of the legal requirements and guidelines which influence the content of the package leaflet. Table 7 provides an overview of the internet sources which were found for use in the analysis of the package leaflet and templates from selected European and non-European countries. Although Germany and the United Kingdom are both in the European Union, where the QRD template is applied, both countries were included, to examine country specific regulations and guidelines which influence the content and appearance of the package leaflet in addition to the QRD template.

Table 7: Internet sources used to gain information on patient information, template structure and content in selected countries

Country/Economic entity	Internet sources
European Union	- European Medicines Agency (EMA)[58] - Heads of Medicines Agency (CMDh)[68] - EUDRALEX[69]
Germany	- Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)[70] - German laws available on the internet[71]
United Kingdom	- Medicines and Healthcare products Regulatory Agency (MHRA)[72] - UK Legislation in internet[73]
Australia	- Australian Government. Department of Health and Ageing, Therapeutic Goods Administration[74] - Commonwealth numbered regulations[75] - Australian self-medication industry[76] - Australian Government Common Law[77] - Medicines Australia[78]
New Zealand	- New Zealand legislation in internet[79] - Medsafe website[80]

Country/Economic entity	Internet sources
The United States of America	- U.S. Food and Drug Administration (FDA)[81] - U.S. Government Printing Office Federal Register[82] - Justia U.S. Law[83]
Switzerland	- Schweizerisches Heilmittelinstitut. Swissmedic[84] - Schweizerisches Eigenossenschaft[85]

4.3.1 United Kingdom: Historical development and documents influencing the content of the package leaflet

In the United Kingdom, some form of medicine regulation has existed since the time of King Henry VIII, but it was in 1971 that a comprehensive regulatory system was first introduced[86]. The package leaflet in the UK is influenced by legally binding documents resulting from EU Directives and UK law as well as non-legally binding guidance documents (table 8).

The Medicines act of 1968[87] was brought in force to govern the manufacture and supply of medicine[87] and subsequently the Misuse of Drugs Act was implemented in 1971[88] to control the use and supply of narcotic drugs and psychotropic substances. Two executive agencies were responsible for overseeing and enforcing the legislation: the Medicines Control Agency (MCA) and the Medical Devices Agency (MDA), which in April 2003 merged to become the Medicines and Healthcare Products Regulatory Agency (MHRA).

The Medicines Act 1968[87] controls manufacture, sale, supply and importation of medicinal products into the UK. Three categories of medicine are defined: prescription only medicines which are only available from a pharmacist, pharmacy medicines available only from a pharmacist but without a prescription, and general sales list medicines which can be bought from any shop without a prescription.

The Medicines Act 1968[87] describes in section 86 that the appropriate ministers may make regulations which impose the requirement of a package leaflet if they consider it necessary. The amendment in 1994 to the Medicines Act 1968[89] inserted a new subsection in section 86 that no medicinal product can be supplied unless it contains a leaflet providing specific information. The content of the package leaflet in the United Kingdom was regulated by the introduction of the Medicines (Leaflets) Regulations 1977[90] which set out in the attached schedule the 'Particulars to be included in leaflets' which included certain European Community obligations under Council Directive 75/319/EC[34].

Table 8: Documents influencing the content of the package leaflet in the United Kingdom

Legally binding documents/regulations	Non-legally binding documents
European Directives: - Directive 2001/83/EC[39] as amended by Directive 2004/27/EC[24]	***European specific guidance documents*** - Guideline on the Readability of the label and package leaflet of medicinal products for human use[38] - Guideline on the packaging information of medicinal products for human use authorised by the community[91] - QRD human product information templates[65] - Council of Europe. Standard Terms. Pharmaceutical dosage forms, routes of administration, containers. 5th Edition[92] - EMA Quality review of Documents: Reference documents and guidelines[93] - Volume 3b Guidelines. Excipients in the label and package leaflet of medicinal products for human use (July 2003)[94]
UK laws: - Medicines Act 1968[87] - The Medicines Act 1968 (Amendment) (No.2) Regulations 1994[89] - The Medicines (Leaflets) Regulations 1977[90] - The Medicines (Leaflets) Amendment Regulations 1992[95] - The Medicines for Human use (Marketing Authorisations Etc.) Regulations 1994[96] - The Medicines for Human Use (Marketing Authorisation Etc.) Amendment Regulations 1998[97] - The Medicines (Codification Amendments Etc.) Regulations 2002[98] - The Medicines for Human Use (Marketing Authorisations Etc.) Amendment Regulations 2003[99]	***UK specific guidance documents*** - MHRA. Guidance on patient information leaflets. Always read the leaflet[101] - MHRA. Glossary of Medical Terms in Lay Language[102] - MHRA. Can you read the leaflet? A guideline on the usability of the patient information leaflet for medicinal products for human use[103] - MHRA. Signposting from the patient information leaflet to additional sources of information and other services[104] - MHRA. Guidance on communication of risk in patient information leaflets[105] - MHRA. Further guidance on designing patient information leaflets and how to achieve success in user testing[106]

Legally binding documents/regulations	Non-legally binding documents
- The Medicines (Marketing Authorisations and Miscellaneous Amendments) Regulations 2004[100]	

The Amendment to the Medicines (Leaflets) Regulations in 1992[95] implemented in part Council Directive 92/27/EC[25]. The regulations defined that the leaflet should be drawn up in accordance with the summary of product characteristics, described additional requirements for form and the content of the leaflet and imposed special requirements for the leaflets of radiopharmaceuticals. The Medicines for Human use (Marketing Authorisations Etc.) Regulations 1994[96] fully implemented the requirement for detailed information to accompany medicines into UK legislation. The Medicines for Human Use (Marketing Authorisation Etc.) Amendment Regulations 1998[97] and 2003[99] specified new necessary warnings for the package leaflets for selected active ingredients. The Medicines (Codification Amendments Etc.) Regulations 2002[98] served to amend the Medicines Act 1968[87] and fully applied European Council Directive 2001/83/EC[39] to UK legislation. The Medicines (Marketing Authorisations and Miscellaneous Amendments) Regulations 2004[100] implemented Directive 2004/27/EC[24] of the European Parliament and of the council into UK Drug Law. The explanatory note in this amendment specifically mentions the provisions now required that the package leaflet '*must reflect the results of consultations with target patient group*' to comply with Article 59 (1) of the Council Directive 2001/83/EC[39]. When the amendment came into force on January 1st 2005 in the UK it became a legal requirement for every product with a marketing authorisation on this date, that all marketing authorisation holders submit applications to update marketing authorisations with an approved patient information leaflet by July 1st 2008[100].

The Patient Information Quality Unit which is part of the Vigilance and Risk Management of Medicines Division of the MHRA is responsible for approving these patient information leaflets. The MHRA provides numerous guidance documents on its webpage to aid the marketing authorisation holder in writing the patient information leaflet. The use of these numerous guidance documents, which are not legally binding, maintains an element of flexibility which is not the case with the formal legal directives. No template for the package leaflet other than that in the Readability Guideline 1998[36] or the QRD template has been developed or used in the United Kingdom.

4.3.2 Germany: Historical development and documents influencing the content of the package leaflet

Due to regulations to create a united Europe, the Federal Ministry of Health was founded in Germany in 1961. The German Drug Law (AMG) of 1976[107], which came into force on January 1st 1978, made the

inclusion of a package leaflet compulsory and defined which information should be contained within this document[108]. In a second amendment of this ruling in 1986, the readability of the package leaflet was already starting to be considered: before the list of required information, an additional statement was included stating that the information should be '*allgemeinverständich*'[32] (generally comprehensible). The role of the summary of product characteristics for medical professionals was also more clearly defined. In 1994, the fifth amendment to German Drug law was used to implement European Council Directive 92/27/EEC[25] while the 14th amendment in 2005 put Directive 2004/27/EC[24] into practice. This 14th amendment enforced major structural changes in the contents of the package leaflet and made user-testing a requirement for medicines receiving marketing authorisation after September 2005[109].

It is not only European Guidelines and German Drug Law which directly influence the contents of the package leaflet in Germany, but also several other legally binding documents. The '*Arzneimittel-Warnhinweisverordnung*'[110] (regulation for warning notices on medicines) determines warnings to be included on the immediate inner packaging, outer packet and in the package leaflet for products containing ethanol and tartrazine. '*Verordnung über die Angabe von Arzneimittelbestandteilen*'[111] (regulation for declaration of certain components in medicines) clarifies how certain buffers, colourings, preservatives, aromas and odorants should be declared while the '*Bezeichnungsverordnung*'[112] (denotation regulation) defines the names of ingredients and excipients used in medicinal products.

The '*Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM))'* (Federal Institute for Drugs and Medical Devices) is the responsible authority for approving the patient information leaflets supplied with a medicine in Germany. BfArM additionally publishes numerous documents which should be used by the marketing authorisation holder for the product information such as '*Mustertexte*'[59] (sample texts) contained in a data base for many commonly used active ingredients and the '*Besonderheitenliste des BfArM*'[113] which is based on the Excipients Guideline published by the European Commission[94]. However the sample texts are going to be replaced by '*Referenztexte'* (reference texts) which are basically the Summary of Product Characteristics and package leaflet from the medicine originator[114].

The introduction of strengthened ruling regarding doping has also influenced the package leaflet in Germany. The '*Gesetz zur Verbesserung der Bekämpfung des Dopings im Sport (Anti-Doping Gesetz)*'[115] (law to improve the fight against doping in sports**)** which came into force in November 2007 made inclusion of a warning statement relating to the type of substance contained in the product mandatory - some doping substances can cause severe danger to health. The appendix contained in the '*Übereinkommen vom 16. November 1989 gegen Doping*'[116] (convention against doping from November 16th 1989) provides a list of prohibited substances. The World Anti-Doping Agency (WADA) publishes an

international standard of prohibited substances annually[117]. Table 9 summarises the documents influencing the package leaflet in Germany.

Table 9: Documents influencing the contents of the package leaflet in Germany

Legally binding documents/regulations	Non-legally binding documents
European Directives: - Directive 2001/83/EC[39] as amended by Directive 2004/27/EC[24]	***European specific guidance documents:*** as listed in table 8
German laws: - *'Anti-Doping Gesetz'*[115] (Anti-doping Law) - *'Arzneimittelgesetz'*[107](German Drug Law) - *'Arzneimittel-Warnhinweisverordnung'*[110] (Regulation for warnings notices on medicines) - *'Verordnung über die Angabe von Arzneimittelbestandteilen'*[111] (Regulation for declaration of certain components in medicines) - *'Bezeichnungsverordnung'*[112] (Regulation regarding the names of ingredients for medicinal products)	***Germany specific guidance documents:*** - Recommendations from BfArM for the presentation of package leaflets[118] - *'Wortlaut der für die Packungsbeilage vorgesehenen Angaben (kommentierte Fassung, Januar 2007)'*[119] (commented template for a package leaflet from BfArM) - *'BfArM Beschreibung der Häufigkeiten von Nebenwirkungen'*[120] (BfArM description of the frequency of side effects) - *'BfArM Mustertexte'*[59] (sample texts) - *'Besonderheitenliste des BfArMs'*[113] (excipients list)

The first template for use for package leaflets with headings, standard statements and explanatory notes was initially produced in Germany in 1993[30]. The document was named '*Anleitung zur Erstellung einer Gebrauchsinformation'* (Guidance for the preparation of a package leaflet) and was prepared according to European Directive 92/27/EEC[25]. The main purpose of the guideline was to provide for a package leaflet which conformed to the legal regulations with patient suitable wording. This guidance document was published a year later in 1994 by the BfArM as the '*Erste Empfehlung zur Gestaltung von Packungsbeilagen'*[121] (first recommendations for the design of package leaflets). The content and order of information was as required by German Drug Law which reflected European ruling at the time. This guideline was updated in 2002[122] and included recommendations on how to design the leaflet and make it more user friendly which were provided on the basis of a translation of the model leaflet and advice contained in the first Readability Guideline[36]. A distinction was also made in the guidance document between prescription only and OTC medicines and it included a general introductory text at the start of the

leaflet similar to today's versions of the QRD template. This template was again updated in 2007 by the BfArM and published on their website[119].

4.3.3 Legal requirements and guidelines influencing the content of the package leaflet in Switzerland

At the beginning of the last century, control of pharmaceuticals was regulated by the individual cantons in Switzerland[123]. In 1934, a central office was set up in Bern known as the '*Interkantonale Kontrollstelle (IKS)*' (Intercantonal Board of Control) which assessed medicines, and carried out laboratory investigations, as well as being an information point for authorities, doctors and pharmacists. Swissmedic, which began its operations in 2002, took over from the IKS. It is currently the competent authority in Switzerland responsible for authorising, licensing and supervising therapeutic products.

The '*Bundesgesetz über Arzneimittel und Medizinprodukte* (*Heilmittelgesetz*)'[124] (Swiss Drug Law), which came into force in 2002, regulates the marketing authorisation and distribution of pharmaceuticals in Switzerland. In addition, the '*Verordnung des Schweizerischen Heilmittelinstituts über die Anforderungen an die Zulassung von Arzneimitteln (Arzneimittel-Zulassungsverordnung- AMZV*)'[125] (Regulation for the approval of marketing authorisation for pharmaceuticals) and the '*Verordnung über die Arzneimittel (Arzneimittelverordnung, VAM)*'[126] (Pharmaceuticals regulation) provide additional rulings based on the Swiss Drug Law). The Pharmaceuticals regulation defines five distribution categories - A to E - for pharmaceutical products in Articles 23 - 27. Categories A and B are for prescription only medicines, categories C and D are for medicines available without prescription but where expert advice is needed, for example from a pharmacist, and E is for medicines which can be bought over-the-counter without any specialist guidance.

Inclusion of a package leaflet has been mandatory since Swiss Drug Law[124] came into force. This patient information must be published in the three official languages i.e. German, French and Italian and according to Article 16 of this law, should continually be updated according to current scientific knowledge[125,126]. In 2004, Swissmedic introduced the regulation that the patient information had to be published electronically[127].

The AMZV[125] stipulates in Article 14 in connection with appendix 5.1 the order of sections which must be contained in the patient information and their content in the form of heading titles and fixed statements. Different mandatory statements must be included for prescription and OTC medicines. Products containing alcohol must include an extra warning in the package leaflet regarding the percent of alcohol, and this is detailed in appendix 2 of the AMZV[125]. The European Excipients Guideline is not applicable

for use in Switzerland and declaration of certain specific excipients is defined in appendix 3 of the AMZV[125]. Here preservatives, antioxidants, colourings, sweeteners and flavour enhancers are named which must be stated on the container, outer packet and in the information on the medicinal product. Products to be used cutaneously, on mucous membranes or the eyes must also declare lanolin and its derivatives, lauryl sulfate and its salts, macrogols up to a molecular mass of 900 and propylene glycol.

The requirements for the patient information of homeopathic or anthroposophic medicines, traditional herbal medicinal products and Asiatic drugs are defined in appendices 5.2, 5.3 and 5.4 respectively in the AMZV[125]. Here extra fixed statements appropriate for the type of product are included. The legally binding and guidance documents influencing the content of the information in the package leaflet in Switzerland are summarised in table 10.

Table 10: Documents influencing the content of the package leaflet in Switzerland

Legally binding documents/regulations	**Non-legally binding documents**
- '*Bundesgesetz über Arzneimittel und Medizinprodukte (Heilmittelgesetz)*'[124] (Drug law) - '*Verordnung des Schweizerischen Heilmittelinstituts über die Anforderungen an die Zulassung von Arzneimitteln (AMZV)*'[125] (Regulation for the approval of marketing authorisation for pharmaceuticals) - '*Verordnung über die Arzneimittel (Arzneimittelverordnung, VAM)*'[126] (Pharmaceuticals regulation) - '*Mustertexte für rezeptpflichtige NSAR. Patienteninformation (Abgabekategorie B)*'[128] (Sample text for prescription only NSAR. Patient information)	- '*Merkblatt: Erläuterung zur Patienteninformation*'[129] (Information sheet: explanations for patient information)

In Switzerland, the '*Merkblatt: Erläuterung zur Patienteninformation*'[129] (Information sheet: explanations for patient information) is published by Swissmedic. This document can be considered as a template as the headings are given as required in the relevant legislation (AMZV[125]), with additional information on how best to fill in the section. The first version of this information sheet was made available in August 2010[130] and was developed according to appendix 5.1 of AMZV[125] and a connected publication in the Swiss Medical Journal from 2002[131]. The guidelines which were implemented in the information sheet were

already part of Swiss legislation which had been in force since 2001. Since 2010, the information sheet has been revised four times for editorial modifications or to take current legal requirements into account. The most recent information sheet was published in November 2011[129]. Four different templates are provided in the information sheet for prescription and OTC medicines which are either classed as 'normal' medicines, homeopathic and anthroposophic medicines, traditional herbal medicines and Asiatic drugs without an indication. Many of the statutory statements, which are often over 20 words in length, from the AMZV[125] are identical for all four classes of medicine although product specific sentences are also included. In a similar manner to the Readability Guideline, it is suggested that foreign words and specialist terms should be avoided and where their use is unavoidable, they should be explained.

In a similar fashion to the German sample texts published by BfArM[59], Swissmedic published sample texts in 2010 for prescription only NSAR (non steroidal antirheumatics) and NSAR intended for self-medication[128,132]. Two versions of each text were published - one for health professionals and the other for patients. Whereas the German sample texts provide a complete text where the marketing authorisation holder need only insert their own product name, the Swiss version is less extensive, especially for prescription only NSAR[128] - here, only the text which is mandatory for the patient information is listed. The text version for NSAR for self-medication[132] has a more similar format to the German texts where almost the complete content of each section is described with gaps left in the headings for insertion of the product name.

4.3.4 Regulations and history of patient information and the development of Consumer Medicine Information (CMI) in Australia

Medicines in Australia are classified into three categories: registered medicines (prescription and non-prescription), listed medicines (most over-the-counter medicines) and complementary medicines (vitamin, mineral, herbal, aromatherapy and homeopathic products). Before a drug can be brought onto the market in Australia, it must be evaluated by the Therapeutic Goods Administration (TGA). This is the regulatory authority of the Australian Government Department of Health and Ageing for therapeutic goods[133]. The TGA is responsible for ensuring that therapeutic goods (medicines and medicinal devices) are safe and suitable for their intended purpose. The Therapeutic Goods Act was first introduced in Australia in 1989[134] and had the objective of maintaining a national system of controls relating to the quality, safety, efficacy and timely availability of therapeutic goods either used in or exported from Australia[134]. This act was amended in 1991 following the release of a report by Professor Peter Baume[135] which also resulted in the same year in a reorganisation of the functions of the TGA. The Baume report was commissioned by the Minister for Aged, Family and Health Services to conduct an inquiry into the access to drugs and the reform of the drug evaluation process in Australia[136]. Following the release of the 232-page report, the

Government announced that Professor Baume's recommendations would be adopted as a package. Before the Baume Report, nearly all applications for prescription medicines were reviewed by the Australian Drug Evaluation Committee (ADEC)[137]. The Baume Report was commissioned due to the perceived dissatisfaction with this drug evaluation system, the main criticism involving the timely availability of drugs. The TGA did not meet its own performance targets, the ADEC process itself was a source of delay and there were holdups in the approval process following meetings of the ADEC. The recommendations of the Baume Report aimed to improve the evaluation process for prescription drugs while still maintaining public protection[137]. The amendment to the Therapeutic Goods Act 1989 therefore included time limits for the completion of evaluations of applications of certain drugs.

In response to lobbying by consumer groups who called for improvements in the way that medicines were prescribed, dispensed and used, the Commonwealth Government established two advisory groups around the same time; the Pharmaceutical Health and Rational use of Medicines (PHARM) Working Party and the Australian Pharmaceutical Advisory Council (APAC)[138]. The PHARM went on to formulate the Quality Use of Medicines (QUM) policy in 1992 which encompassed a partnership between government, industry, consumers and health professionals.

The Baume Report 1991 recommended that a patient information document be developed for all prescription medicines[135]. These patient information documents were originally known as Consumer Product Information Leaflets, but this was later changed to Consumer Medicine Information (CMI) to reflect the fact that the document was intended to provide the user with information about a medicine[139]. This was one of the first achievements of the new partnership under the QUM, that consumers worked with the government and pharmaceutical industry to produce these leaflets[138]. The term Consumer Medicine Information (CMI) was first utilised in New Zealand and then adopted in Australia[140]. CMIs became mandatory for all new prescription medicines from January 1st 1993, and in January 1st 2003 was extended to cover all prescription medicines as regulated by the Therapeutic Goods Regulation act[134]. The requirement for a CMI for pharmacist-only medicines was decided in July 1995 and, as of January 1st 2004, all pharmacist-only medicines were obliged to have a CMI. Schedules 12 and 13 of the Therapeutic Goods Regulations act define the content of the patient information document for prescription and non-prescription medicines respectively[134]. The requirements stipulated by Australian law are very similar to those laid down in the European Directive 2001/83/EEC, although the information does not need to appear in the order outlined in the regulation, contrary to Article 59 in the European Union which determines the order. Australian CMIs must also include the expected effect of using the medicinal product and whether its use has habit forming potential, neither of which is reflected in Article 59. However, since publication

of QRD template version 8, the template allows information to be included on the benefits of using the medicine.

Each medicine, whether prescription or pharmacist-only, must also have a Product Information (PI) intended for use by health professionals. Both PI and CMI are written by the pharmaceutical company responsible for the medicine and are subsequently approved by the TGA. The contents of the PI are similar to the European SmPC and include amongst others the name of the medicine, description, pharmacology, clinical trials, indications, precautions, adverse effects, dosage and overdosage. All CMIs must be consistent with the PI but there is no legal requirement that all information contained in the PI must be contained in the CMI[140].

Most CMIs are leaflets contained in the package as an insert while others are available on an electronic database which can be accessed by pharmacists, or as a leaflet which the pharmacist can give to the consumer. In 1995, the CMI content/Quality Assurance Reference Group was established to assess CMIs and provide advice on their development[141]. Core CMIs are available for a large range of active ingredients such as ACE inhibitors, diuretics, numerous antibiotics and NSAIDs. The first core CMIs for prescription medicines became available in 1993. Most similar to the European QRD template is the general core CMI for Product X which was first finalised in March 2001[142]. The current version published in August 2005 can be downloaded from the Medicines Australia webpage[143]. In addition to the required sections, which are described in the Therapeutic Goods Regulations[134], the CMI includes a selection of standard statements under each section heading and advice on how best to present information. Table 11 provides a summary of legally binding documents and guidelines influencing the package leaflet in Australia.

Table 11: Documents influencing package leaflets in Australia

Legally binding documents/regulations	**Non-legally binding documents**
- Therapeutic Goods Regulations 1990[134] (Schedule 12 for prescription medicines and Schedule 13 for pharmacist only). - Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)[144]. - TGA Approved Terminology for Medicines[145].	- Core CMIs available from Medicines Australia[143]. - Writing about medicines for people 3rd Edition[146] - Vocabulary for consumer medical information (CMI) available from Medicines Australia[147].

4.3.5 Regulations and history of patient information and Consumer Medicine Information (CMI) in New Zealand

In New Zealand, the New Zealand Medicines and Medical Devices Safety Authority (Medsafe) is responsible for regulating products for therapeutic purpose which includes medicines, herbal remedies and medical devices. The Medicines Act 1981[148] and the Medicines Regulations 1984[149] are administered by Medsafe. The Medicines Act 1981[148] controls the manufacture and distribution of medicines and related products, the conduct of clinical trials and the advertising and sale of medicines, while the Medicines Regulations 1984[149] specify amongst others, the requirements for advertisements, licences, data sheets, labelling and packaging of medicines and related products. The Medicines Act 1981[148] established a classification system for prescription only medicines, restricted medicines or pharmacy only medicines, while the Medicines Regulations 1984[149] lists the medicines in these categories in Schedule 1 parts 1 to 3 respectively.

There is no legal requirement for pharmaceutical companies in New Zealand to produce patient information leaflets, although if the required information stipulated in Regulation 13 of the Medicines Regulations 1984[149] for the labelling of the product cannot be present on the container of the medicine, for example, if the container is too small, a separate information sheet must be provided for the patient. Instructions for dosage, indication and ingredients are described on the container but contraindications, side effects or interactions with other medicines are not mentioned. However, consumers in New Zealand can, in addition to advice provided by their doctor, refer to the Consumer Medicine Information (CMI) which is very similar to that seen in Australia. For a great number of active ingredients, CMIs can be accessed on the Medsafe website and were introduced in New Zealand from around 1998[150]. The pharmaceutical companies are responsible for producing the CMI which contains detailed advice on how to use the medicine, side effects etc. Though there is no legal requirement for a CMI to be produced for each product, where a CMI is present it must be prepared using the guidelines set by Medsafe which are contained in Part 10 of the Guideline on the Regulation of Therapeutic Products in New Zealand[151]. This guideline was developed in collaboration with doctors, pharmacists and consumers. Part 10.4 contains the 'Template for preparing CMI for New Zealand Consumers'[152]. The template for preparing CMI is for both prescription and non-prescription drugs and makes no distinction between the two categories, neither for headings nor standard statements which are present. Brief advice is included on what information should be included under each section heading.

Pharmaceutical companies are required to prepare data sheets for all prescription and pharmacist-only medicines in accordance with the Medicines Regulations 1984[149] and Medsafe regulatory guidelines. General sales medicines are not required to have a data sheet. The data sheets greatly resemble the

European Union SmPC and can be viewed on the Medsafe website. Table 12 provides a summary of documents and guidelines influencing the package leaflet in New Zealand.

Table 12: Documents influencing package leaflets in New Zealand

Legally binding documents/regulations	Non-legally binding documents
- No legal requirements to produce patient information leaflets	- Guideline on the Regulation of Therapeutic Products in New Zealand[151] - Template for preparing CMI for New Zealand Consumers'[152]

4.3.6 Regulations and history of patient information and templates in the United States

Written consumer information takes three main forms in the United States for prescription medicines, and includes the patient package insert (PPI), medication guides (usually called MedGuides) and consumer medication information (CMI)[153]. Over-the-counter medicines are not required to contain a package leaflet but must abide by the drug labelling ruling described later[154]. The situation for prescription only medicines is summarised in table 13.

Table 13: Summary of consumer information for prescription medications in the United States

	Consumer medication information (CMI)	Medication guide	Patient package insert (PPI)
Availability	Dispensed voluntarily by the chemist	Must be dispensed by the chemist	Contained in the packet
For which medicines?	All new prescription medicines	Prescription medicines which the FDA decides have a serious and significant health concern	Oral contraceptives and estrogen containing products. FDA or drug companies can decide on additional PPIs
Who writes it?	Organisations other than the drug's manufacturer	Drug company	Drug company
Is it FDA approved?	No	Yes	Yes

The Food and Drug Administration (FDA) is the agency within the US Department of Health and Human Sciences responsible for protecting public health with respect to safety and effectiveness of drugs,

vaccines, medical devices and cosmetics to name but a few. Its origins can be traced back to around 1848 although it was not known under its present name until 1930[155]. The code of federal regulations is the codification of general and permanent rules published in the federal register by the executive departments of the United States government. Title 21 is the portion of this legislation which governs food and drugs. Proposed rules in the United States are first published for public comments which are then analysed resulting if necessary in the rule being modified, before the final rule is published in the federal register and subsequently incorporated into the next edition of the code of federal regulations.

The development of mandatory patient information in the United States began in 1968 when federal regulations demanded that a warning was included on the packaging of isoproterenol inhalation medication that excessive use can cause breathing difficulties[156]. However, this advice could be included on the immediate container label or in the form of a printed statement in the package. This was followed in 1970 by the requirement from the FDA that patient information should be dispensed with (either in the packet or as an accompanying document issued to the patient) oral contraceptives[157] and in 1977 for estrogens[158]. The relevant legislation defined that the patient package insert should detail risk and benefits of birth control pills. In the 1970s the FDA began evaluating the usefulness of patient labelling for prescription drugs, which resulted in a number of regulatory steps to ensure the availability of written consumer information[159]. Regulations were proposed in 1979 that would require manufacturers or distributors to prepare written PPIs for prescription drug products generally, and these were to be distributed by the persons dispensing the medication[160]. The PPI was to contain a summary of information about the product and detail on how it should be used, as well as information on side effects, precautions and interactions. In 1980, a final regulation establishing requirements and procedures for the preparation and distribution of PPIs was published and in the same year, the FDA provided draft guideline PPIs for ten widely used prescription drugs or drug classes such as benzodiazepines and thiazide[160]. In 1982, the FDA revoked these regulations, partially due to assurances from the private sector and pharmaceutical companies who felt that the goals of this final rule could be met more successfully without the restrictions of a regulation[159]. To coordinate these efforts, the voluntary organisation known as the National Council on Patient Information and Education (NCPIE) was formed.

A survey of estimated distribution rates carried out by the FDA however revealed that significant numbers of patients still did not receive information with their medications and in 1995 the FDA was compelled to propose the 'Prescription Drug Product Labeling; Medication Guide Requirements'[160] in order to improve the quality and distribution of patient information. The FDA stated in this planned ruling that '*Inadequate access to appropriate patient information is a major cause of inappropriate use of prescription medications, resulting in serious personal injury and related costs to the health care system*'[160] and

therefore specific time frames and goals were laid down to ensure that by the year 2006, 95 percent of people receiving new prescriptions would receive useful written information. The ruling also required manufacturers to prepare FDA approved medication guides for specific prescription products which the FDA had determined to have serious and significant public health concerns.

However, calls from the private sector resulted in the congress enacting the public law 104 - 180[161] whereby the FDA was prohibited from taking regulatory steps to specify a uniform content or format for written information. However, the goals and timeframes from the FDA proposed 1995 ruling were adopted but the main responsibility of improving performance was moved to the private sector. Enacting of public law 104 - 180 also resulted in a Steering Committee being created which developed the '*Action Plan for the Provision of useful Prescription Medicine Information*'. This action plan described criteria to evaluate whether a particular piece of written medication information is useful to consumers[162].

The final ruling on medication guide requirements for prescription drugs was published by the FDA in 1998[163] which described the content of such a guide. The guides prepared by the manufacturer are approved by the FDA and are required to be distributed with each prescription medicine. The Food and Drug Administration Amendments Act of 2007[164] created a new section 505 which is used by the FDA to implement a tight timeframe for the development of a medication guide and changes to labelling based on new safety-related information.

In December 2000, the FDA proposed to amend its regulations governing the format and content of labelling for human prescription drug products[165]. However, it took some years for the major revision to the initial guidelines for this labelling to be enforced in 2006 in the Code of Federal Regulations Title 21[166]. The newly designed leaflet enclosed in the package was to provide healthcare practitioners with the most up-to-date information in an easy-to-read format to draw attention to the most important pieces of information[167]. Any FDA approved patient labelling must be reprinted or accompany the labelling. The most significant changes were inclusion of a box called '*Highlights*' which summarised the most important information and a table of contents for easy reference. The FDA issued four guidance documents in 2006 in coordination with the publication of the final rules, which are not legally enforceable but should be viewed as recommendations. These papers described the adverse reactions [168]and clinical studies section[169] as well as the warnings and precautions, contraindications and boxed warnings section (draft)[170]. The fourth guidance document, which was a draft, provided information on how the new content and format requirements should be implemented[171]. Sample package leaflets for four fictitious drugs were also published by the FDA to demonstrate the new format. In 2009 a fifth draft paper was released on the clinical pharmacology section[172], and in 2010 a guidance document followed on the

dosage and administration section[173]. Table 15 provides a summary of legally binding documents and guidelines influencing consumer information on medicines in the United States.

Table 14: Documents influencing consumer information on medicines in the United States

Legally binding documents/regulations	Non-legally binding documents
Leaflet for prescription medicines for healthcare practitioners: - Code of Federal Regulations Title 21, Part 201 Labeling Requirements for Prescription Drugs and/or Insulin[166]. ***Medication Guides:*** - Code of Federal Regulations Title 21, Part 208; Medication Guides for Prescription Drug Products[163]. - Food and Drug Administration Amendments Act (2007)[164] ***OTC Medicines:*** - Code of Federal Regulations Title 21, Part 201 Labeling Requirements for Over-the-Counter Drugs [154]	***Package leaflet for prescription medicines:*** Guidance for Industry documents from U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER): - Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products - Content and Format[169]. - Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products - Content and Format[168]. - Warnings and Precautions, Contraindications and Boxed Warnings Section (draft)[170]. - Implementing the New Content and Format Requirements[171] - Clinical Pharmacology Section[172] - Dosage and Administration Section[173] - U.S. Department of Health and Human Services; Food and Drug Administration; Center for Drug Evaluation and Research (CDER); Center for Biologics Evaluation and Research (CBER); Center for Veterinary Medicine (CVM); Center for Devices and Radiological Health (CDRH). Guidance for Industry. Presenting Risk Information in Prescription Drug and Medical Device Promotion (Draft)[174]

Legally binding documents/regulations	Non-legally binding documents
	Consumer Medication Information: - Useful Written Consumer Medication Information (CMI)[159] ***OTC medicines:*** - U.S. Department of Health and Human Services; Food and Drug Administration; Center for Drug Evaluation and Research (CDER). Guidance for Industry. Labeling OTC Human Drug Products Using a Column Format[175] - U.S. Department of Health and Human Services; Food and Drug Administration; Center for Drug Evaluation and Research (CDER). Guidance for Industry. Labeling OTC Human Drug Products - Questions and Answers[176]

4.4 Comparison of QRD template version 9 to non-EU package leaflet templates

4.4.1 Comparison of QRD template version 9 to the Swiss package leaflet template

Although the Swiss package leaflet must be printed in the three main official languages spoken in Switzerland, the template is only provided in German, in contrast to the QRD template version 9 which is published in the languages of every country where it is intended to be used. Table 15 shows the contents of the Swiss template in comparison to QRD template 9. Although the QRD template 9 contains fewer headings than the Swiss template, the actual order of the information contained is very similar.

The Swiss package leaflet template starts with a fixed text information box that distinguishes between prescription and non-prescription medicines with similar wording to that of the QRD template 9. Additionally the terms '*Drogerie/Drogistin'* (drug store/druggist) are regularly included for non-prescription medicines of the category D which can be sold in drugstores in Switzerland. These are specialist shops which sell cereals, health foods, cosmetics and wellness products. Although the headings are numbered, the Swiss patient information contains no list of contents in contrast to the QRD template 9. Subheadings are not suggested in any section in Switzerland. The order of section 1 and 2 of the Swiss template can be swapped on request by the marketing authorisation holder and not all sections which are described in Article 14 of the *AMZV*[125] are mandatory. Section 4 '*Was sollte dazu beachtet werden*?'

(What should be taken into consideration?) is not obligatory in Switzerland and should only be included when necessary or useful to deliver information to the patient in addition to that regarding the medical treatment. Here is meant dietary measures, general codes of behaviour such as using mosquito repellents in addition to malarial drugs and influence of the medicine on urine, stool or contact lenses. However, this section must be included when a relevant warning is required for diabetics describing the bread units contained in the product. Addition of such 'behavioural' information is not provided in the QRD template 9 although bread units may be included where relevant.

In the Swiss template, instructions on what to do in the event of an overdose, in the case of a forgotten dose, or abruptly discontinuing treatment, must only be included if they are considered necessary and meaningful. The section for pregnancy and breast feeding can also be omitted in Switzerland, for example with products specifically for use in children or only in men. Although the brackets in the QRD template 9 mean that exclusion of the three sections - overdose, forgotten dose or stopping treatment - is possible, omission of the section on pregnancy and breast-feeding is not allowed. In Switzerland, section 15 '*Herstellerin'* (manufacturer) is also not obligatory as in the QRD template 9.

Compulsory statements for alcohol and azo dye containing products are present in the Swiss template as regulated by the AMZV[125]. Warnings for these ingredients are regulated in the European Commission's Excipients Guideline[94] rather than a directive. In section 6 '*Wann ist bei der Einnahme/Anwendung von … Vorsicht geboten*?' (When should care be taken during use of …?) patients who are allergic to azo dyes, acetylsalicylic acid and prostaglandin inhibitors are warned not to take the product. A fixed statement describing the side effects which can be caused by azo dyes is also mandatory in section 9. For alcohol containing products, sections 6, 10 and 11 of Swiss package leaflets must all include relevant statements as specified in appendix 2 of the AMZV[125].

Table 15: Main headings to be used in the Swiss package leaflet template for prescription and OTC medicines from AMZV in comparison to headings (bold type) and subheadings (normal print) from QRD template 9

Swiss template[125]		**QRD template 9**[48]	
Section number	**Section heading**	**Section number**	**Section heading/Subheading**
1	**Information für Patientinnen und Patienten*** (Information for patients)	{(Invented) name strength pharmaceutical form} {Active substance(s)} Information box prescription/OTC medicines and index 'What is in this leaflet'	
2 (a)	**Name des Präparates*** (Name of the product)		
3	**Was ist … und wann wird es angewendet?** (What is …. and what it is used for)	**1**	**What X is and what it is used for**
4	**Was sollte dazu beachtet werden?** (What should be taken into consideration?)	**2**	**What you need to know before you <take> <use> X** Do not <take> <use> X<:> Warnings and precautions Children <and adolescents> Other medicines and X X with <food> <and> <,> <drink> <and> <alcohol> Pregnancy <and> <,> breast-feeding <and fertility> Driving and using machines <X contains {name the excipient(s)}>
5	**Wann darf …. nicht eingenommen/angewendet werden?** (When should … not be taken/used?)		
6	**Wann ist bei der Einnahme/Anwendung von … Vorsicht geboten?** (When should care be taken during use of …?)		
7	**Darf … während einer Schwangerschaft oder in der Stillzeit eingenommen/angewendet werden?** (Can … be used during pregnancy or breast-feeding?)		

Swiss template[125]		**QRD template 9[48]**	
Section number	**Section heading**	**Section number**	**Section heading/Subheading**
8	**Wie verwenden Sie …?** (How should you use …?)	**3**	**How to <take> <use> X** <Use in children <and adolescents>> <If you <take> <use> more X than you should> <If you forget to <take> <use> X> <If you stop <taking> <using> X>
9	**Welche Nebenwirkungen kann … haben?** (Which side effects can … have?)	**4**	**Possible side effects** **<Additional side effects in children <and adolescents>>** **Reporting of side effects**
10	**Was ist ferner zu beachten?** (What else should be taken into consideration?)	**5**	**How to store X**
11	**Was ist in … enthalten?** (What is contained in …?)	**6**	**Contents of the pack and other information** What X contains What X looks like and contents of the pack Marketing Authorisation Holder and Manufacturer This leaflet was last revised in <{MM/YYYY}> <{month YYYY}>.
12	**Zulassungsnummer** (marketing authorisation number)		
13	**Wo erhalten Sie …? Welche Packungen sind erhältlich?** (Where can you get ….? Which packets are available?)		
14	**Zulassungsinhaberin (**Marketing authorisation holder)		
15	**Herstellerin** (manufacturer)		
16	**Diese Packungsbeilage wurde im… (Monat/Jahr) letztmals**		

Swiss template[125]		QRD template 9[48]	
Section number	**Section heading**	**Section number**	**Section heading/Subheading**
	durch die Arzneibehörde (Swissmedic) geprüft. (This package leaflet was last reviewed by the Drug administration authority (Swissmedic) in….)		

* Sections 1 and 2 of the Swiss template may be swapped on request

Headings and fixed text defined in the AMZV[125] for homeopathic and anthroposophic medicines are present in the Swissmedic template for these products and are very similar to those for 'normal' prescription and non-prescription medicines. Section 2 is divided into 2a - Name of the product, and 2b - either homeopathic medicine or anthroposophic medicine, if these terms are not mentioned in the name of the preparation. When describing the indication the product is used for, the patient is informed that according to anthroposophic knowledge of humans and nature, or homeopathic principles, that the medicine can be used for treating the mentioned disorders[125]. Sections 5 and 6 are merged into one section for these types of medicine which then includes all contraindications and precautions. Rubrics which can be omitted and mandatory information for azo dyes, alcohol and diabetics are identical to other medicinal products. Article 14 of the AMZV[125] includes a fixed statement on the side effects section for homeopathic medicines that complaints may temporarily become worse (initial aggravation) and that a doctor should be contacted if the situation persists. The template clearly defines how the active ingredient should be declared to enable easy identification of the raw material.

Traditional herbal medicines such as teas and tea mixtures, where all information needed for use is described on the container, are not required to have a package leaflet. For all others, section 2b states '*Pflanzliches Arzneimittel'* (traditional herbal medicine) which can be omitted if this is contained in the name of the product. In section 3 '*Was ist... und wann wird es angwendet*' (What is .... and what it is used for), fixed text differentiates between whether clinically controlled efficacy studies exist for the active ingredient, or whether the product is traditionally used for the treatment of certain conditions. Sections 5 and 6 are merged into one section. Rubrics which can be omitted and other mandatory information for azo dyes, alcohol and diabetics are identical to those for other medicinal products.

The patient information for Asiatic drugs is not only regulated by the AMZV[125] but also by the '*Verordnung des Schweizerischen Heilmittelinstituts über die vereinfachte Zulassung von Komplementär- und Phytoarzneimitteln (Komplementär- und Phytoarzneimittelverordnung, KPAV'*[177]) (Ordinance of the Swiss Institute of Therapeutic Products concerning simplified Marketing Authorisations for Complementary and Herbal Medicinal Products). The KPAV[177] states that the patient information for Asiatic drugs must contain the information in appendix 5.2 of the AMZV[125] which relates to homeopathic and anthroposophic medicines. Appendix 5.4 of the AMZV[125] contains additional fixed statements which must be used for the three types of Asiatic medicines which are distinguished between, namely traditional Chinese, Tibetan or ayurvedic remedies. Here complete sections of manuscript are provided for the patient information. The Swissmedic template for Asiatic drugs simply refers the reader to the applicable section of the AMZV[125] and he/she is told to use the fixed statements found there. The European Union QRD template 9 does not contain any specific wording variations which should be used for homeopathic

medicines, traditional herbal medicines or Asiatic drugs; however, the QRD template version 3 intended for medicines approved via mutual-recognition, decentralised and referral procedures should be used for these products. National ruling and standard texts do however exist in many countries, for example, in Germany the content of package leaflets for traditional medicines is regulated in § 11 of German Drug Law[107].

4.4.2 Comparison of QRD template 9 to the Australian core Consumer Medicine Information (CMI) template

The core CMI template for product X provides instructions in italics for the CMI writer in a similar manner to the green text seen in the annotated QRD template 9. A three column format is recommended in Australia and under each heading, sample statements in bold type are provided from the second edition of the Usability Guidelines[178] which should be chosen or amended as necessary. These guidelines should continuously be abided by in the CMI and were first developed in 1995 to assist manufacturers when writing their own patient information, and then revised in 1997. A 3rd edition of these usability guidelines was released in 2006 which is only available electronically[146]. The Usability Guidelines provide headings, subheadings, sample statements, and formatting specifications. As in the European Readability Guideline[38], excessive use of the product name should be avoided by using 'your medicine. The terms 'take', 'use', 'having' or 'giving' should be applied according to the type of product and the active voice should be used. It is stated that all instructions should be written in bold. Although these extensive guidance documents, as well as user testing were pioneered in Australia in the 1990s, it is not part of any legislation.

General notes at the start of the CMI mention the use of a glossary of plain English terms for symptoms of a disease and side effects which is contained in a document titled 'Vocabulary for Consumer Medicine Information' (CMI)[147]. This is available from Medicines Australia and the ASMI (Australian Self Medication Industry, established in 1974) and is the main body representing companies involved in the manufacture and distribution of consumer healthcare products in Australia. The vocabulary includes a medical term followed by the consumer meaning, where possible, with alternative explanations or descriptions. However, the use of the terms is voluntary and only meant to provide assistance to the CMI writer. Furthermore, no evidence is provided that these explanations have been tested for comprehensibility.

Table 16: Sections headings and subheadings in the Australian core CMI template in comparison to QRD template 9

CMI heading[143]	**QRD template 9 heading**[48]	**Subheadings in CMI**	**Subheadings in QRD template 9**
What is in this leaflet	What is in this leaflet	----	----
What [Medicine name] is used for	What X is and what it is used for	----	----
Before you take/use/have/are given [Medicine name]	What you need to know before you <take> <use> X	When you must not take it Before you start to take it Taking other medicines	Do not <take> <use> X<:> Warnings and precautions Children <and adolescents> Other medicines and X X with <food> <and> <,> <drink> <and> <alcohol> Pregnancy <and> <,> breast-feeding <and fertility> Driving and using machines <X contains {name the excipient(s)}>
How to take [Medicine name]	How to <take> <use> X	How much to take How to take it When to take it How long to take it If you forget to take it If you take too much (overdose)	<Use in children <and adolescents>> <If you <take> <use> more X than you should> <If you forget to <take> <use> X> <If you stop <taking> <using> X>
While you are using [Medicine name]		Things you must do Things you must not do Things to be careful of Things that would be helpful for ……	

CMI heading[143]	QRD template 9 heading[48]	Subheadings in CMI	Subheadings in QRD template 9
Side effects	Possible side effects	-----	<Additional side effects in children <and adolescents>> Reporting of side effects
After using [Medicine name]	How to store X	Storage Disposal	----
Product description	Contents of the pack and other information	What it looks like Ingredients Manufacturer /Distributor/ Supplier	What X contains What X looks like and contents of the pack Marketing Authorisation Holder and Manufacturer This leaflet was last revised in <{MM/YYYY}> <{month YYYY}>.

Table 16 shows the great similarity between the CMI template and QRD template 9. At the top of the Australian Consumer Medicine Information, the user is presented with the title [Medicine name] followed by 'Name of the active ingredient' and for both, the phonetic pronunciation. The QRD template 9 also starts with the invented name of the product followed by strength and pharmaceutical form. The active substance(s) is written underneath. There is no provision in the QRD template for phonetic pronunciations of these terms.

The Australian CMI does not start with an information box at the beginning of the leaflet for prescription or OTC medicines although the first heading 'What is in this leaflet' does include general information about keeping the leaflet. There is no contents list as in the QRD template 9. The lack of contents list maybe reflects that the sections in the core CMI are not numbered. The Usability Guidelines however, provide an illustrated CMI as an example which has a table of contents but notes that it is not necessary for a CMI of four pages or less[146]. When one is included it is shown under the first heading mentioned above. The main headings presented in the core CMI have been tested by consumers and are therefore strongly recommended to be used by the Usability Guideline[146]. Standard statements contained in the core CMI are optional and should be tailored to fit a certain product.

‘What [Medicine name] is used for’ in the Australian CMI contains information on the therapeutic indications, how the medicine works and the expected effects of the product in a similar manner to the information contained in QRD template 9 section 1 ‘What X is and what it is used for’[48]. Other additional sample statements in the Australian CMI under ‘What [Medicine name] is used for’ concern whether the product is addictive, if the ability to drive is affected and use in children.

‘Before your take/use/have/are given [Medicine name]’ in the Australian CMI[143] includes all contraindications, special warnings and precautions, and interactions with other medicines and is similar to section 2 of the QRD template 9 ‘What you need to know before you <take> <use> X’[48]. Information regarding pregnancy and breast-feeding is also in this section of the CMI although no specific subheading is recommended for these topics in the core CMI template. This is contrary to the current QRD template 9 where the subheading ‘Pregnancy <and> <,> breast-feeding <and fertility>‘ is provided in section 2[48]. A warning is given in this section of the CMI not to use the medicine after the expiry date printed on the pack, which is in contrast to the QRD template 9 where this information is presented in section 5 ‘How to store X’[48]. As a precaution, the Australian user is told in the section ‘Before your take/use/have/are given [Medicine name]’[143] to tell the doctor not only about allergies to other medicines but also to foods, preservatives or dyes which is not reflected in the QRD template 9. However the QRD template mentions at the end of section 2, on the basis of the excipients guideline, excipients contained in the medicine which may cause allergies or side effects. As OTC medicines can be bought in Australia not only from pharmacies, but also from supermarkets or health food shops, consumers are told to tell their doctor or pharmacist if they are taking medicines purchased from any of these locations.

The section titled ‘How to take [Medicine name]’in the Australian CMI is similar in content to section 3 of the QRD template 9 ‘How to <take> <use> X’. A difference between the two templates is that the Australian CMI contains a telephone number for the Poisons Information Centre in the case of an overdose. Telephone numbers for such institutions in the specific case of an overdose are not included in the QRD template 9 in this section although some national authorities request their inclusion such as in Belgium, Finland or Norway[179]. Postal and email addresses, websites and in some cases telephone and fax numbers are however content of section 4 for reporting of side effects in QRD template 9.

The subsequent section in the core CMI template is for ‘While you are using [Medicine name]’ where precautions are described, such as to tell a doctor or dentist before an operation or blood test and to keep to doctors’ appointments. The effects on driving and using machines, and children specific warnings should be included such as riding bicycles or climbing trees. These children specific warnings are not considered in the European QRD template. The precautions described in this section of the CMI are

similar those which are in section 2 of the QRD template 9 under the subheading 'Warnings and precautions'. The CMI also include in this section self-help measures for patients to improve their condition, for example, eating a healthy diet or taking regular exercise. Space for inclusion of such 'behavioural' information is not present in QRD template 9.

The section in the CMI 'While you are using [Medicine name]' is followed by 'side effects' where general statements are suggested to precede the list. Side effects should be listed in order of urgency of the behaviour required, namely most serious first. This is similar to section 4 of the QRD template 9 where the most serious side effects are listed first. Only those symptoms which the consumer can detect and do something about should be included in the CMI.

'After using [Medicine name]' follows the side effect section in the CMI. This is product specific and describes storage and disposal statements. The CMI ends with the 'Product description'. Interestingly, a list of excipients is included which are **not** contained in the product rather than those with known effects as is the case in the QRD template 9. The CMI contains the sentence '*This medicine does not contain lactose, sucrose, gluten, tartrazine or any other azo dyes*' and the writer is instructed to include any others that are appropriate. In Australia, it is not a requirement to list excipients which may affect the safe use of the product in the CMI, but only on the label. This is regulated by the Therapeutic Goods Order No. 69 which was compiled under section 10 of the Therapeutic Goods Act 1989[180], and defines the requirements for labels for medicines. In Schedule 1 of the order, excipients required to be declared on the label of medicines are listed along with the conditions and special labelling requirements.

4.4.3 Comparison of QRD template 9 to the New Zealand core Consumer Medicine Information (CMI) template

The core CMI[152] in New Zealand is very similar to that in Australia making it also very similar to the QRD template 9 as shown in table 17, although the detail provided for the pharmaceutical company on how to fill in the relevant information is very sparse. As seen in the Australian CMI template, under the first heading 'What is in this leaflet' general information is included about keeping the leaflet rather than the contents list as in the QRD template 9. The New Zealand CMI template differs from the Australian CMI in that separate section headings are provided for overdose, sponsor details and date of preparation of the leaflet. This information is integrated under different section headings in the QRD template 9.

Table 17: Sections headings and subheadings in the New Zealand core consumer medicine information (CMI) template in comparison to QRD template 9 headings and subheadings

CMI heading in bold[152]	**QRD template 9 heading**[48]	**Subheadings in CMI**	**Subheadings in QRD template 9**
What is in this leaflet	What is in this leaflet	----	----
What [Trade name] is used for	What X is and what it is used for	----	----
Before you use [Trade name]	What you need to know before you <take> <use> X	When you must not use it Before you start to use it Taking other medicines	Do not <take> <use> X Warnings and precautions Children <and adolescents> Other medicines and X X with <food> <and> <,> <drink> <and> <alcohol> Pregnancy <and> <,> breast-feeding <and fertility> Driving and using machines <X contains {name the excipient(s)}>
How to use [Trade name]	How to <take> <use> X	How much to take When to take it How long to take it If you forget to take it	<Use in children <and adolescents> <If you <take> <use> more X than you should> <If you forget to <take> <use> X> <If you stop <taking> <using> X>
While you are using [Trade name]		Things you must do Things you must not do Things to be careful of	
In case of overdose		If you take too much (overdose)	

CMI heading in bold[152]	QRD template 9 heading[48]	Subheadings in CMI	Subheadings in QRD template 9
Side effects	Possible side effects	----	<Additional side effects in children <and adolescents>> Reporting of side effects
After using [Trade name]	How to store X	Storage Disposal	
Product description	Contents of the pack and other information	What it looks like Ingredients Manufacturer /Distributor/ Supplier	What X contains What X looks like and contents of the pack Marketing Authorisation Holder and Manufacturer This leaflet was last revised in <{MM/YYYY}> <{month YYYY}>.
Sponsor details		----	
Date of preparation		----	

4.4.4 Comparison of QRD template 9 to the different templates used in the Unites States for patient information

4.4.4.1 Analysis of the content of the labelling for prescription medicines in the United States

The new labelling for prescription medicines is not incorporated into the following comparison of templates used in the United States to the QRD template 9, as this information is mainly intended for use by clinical professionals, as detailed pharmacology and patient counselling information sections are included[166]. Details on the regulations regarding prescription medicines were given in section 4.3.6 to provide a better overview of the situation in the United States regarding printed medicine information. The MedGuide and drug facts labelling for OTC medicines can be considered to be templates as set headings are defined as well as the content which should be included. Although the CMI does not take on the form of a template with respect to defined headings, the content and how it should be presented are clearly described although not legally binding[159].

4.4.4.2 Information required in a medication guide (MedGuide)

The Code of Federal Regulations Title 21 Part 208 describes the general requirements for a medication guide[163]. The headings stated in the regulations should be used in the defined order if appropriate to the product. The phonetic spelling of either the brand name or established name should be included. No contents list or numbered sections are contained in the MedGuide in contrast to the QRD template 9. The first heading 'What is the most important information I should know about (name of drug)?' describes the particular serious and significant public health concern that has created the need for the medication guide and statements should inform the patient on how to weigh up the benefits against the risks of using the medicine. Such information is not included in the QRD template 9. In the MedGuide, the headings are all written as a series of questions and clear instructions are given on which statements must be included. The nature of the disease or condition the drug product is intended to treat, as well as the benefits of treating the condition are allowed to be described under 'appropriate circumstances'[163], although these situations are not defined. The QRD template 9 also allows 'on a case-by-case basis' that information on the benefits of the treatment can be included[50].

4.4.4.3 Content of Consumer Medication Information (CMI)

In 2006, the FDA issued a non-binding guideline in collaboration with the Center for Drug Evaluation and Research (CDER) and Center for Biologics and Research (CBER) to assist the writers of Consumer Medication Information (CMI)[159]. CMIs are intended for prescription only drugs and since the FDA does not personally approve this information, the guidance was hoped to help ensure that CMIs are useful to consumers. To this end, the eight criteria developed in the action plan[162] were listed and recommendations to satisfy these criteria were presented. Criteria 1 to 6 involved the contents of the CMI, while 7 and 8 assessed whether the information is scientifically accurate, unbiased and up-to-date as well as being legible and comprehensible to users. The guidelines include no set section headings or subheadings in contrast to the QRD template 9 but rather detailed guidance on how and which information should be presented. It is recommended including all approved indications and contraindications in the package leaflet but not a full listing of all possible side effects. The most serious should appear plus a statement telling patients that the list is not complete. A disclaimer should also be included that the CMI is a summary and does not contain all possible information. The main sections to be included in the CMI are indications, contraindications, directions for use and storage, precautions and side effects which are also contained in the QRD template 9.

4.4.4.4 Information intended for over-the-counter (OTC) medicines

OTC medicines are considered by the FDA to be safe and effective for the general public to use without a prescription. These drugs are not obliged to include a package leaflet but must abide by the Drug Facts

labelling requirements in the Code of Federal Regulations Title 21[154] which were defined by the FDA in 1999[181], whereby information is printed on the immediate packaging or outside container under the heading 'Drug Facts'. The title 'Drug Facts' is compulsory in a standardised format as this is stated to provide an important visual cue for introducing required information. The Drug Facts label is in the form of a template with mandatory headings specified to be written in bold type for inclusion of information on the product's active ingredient(s), indications and purpose, safety warnings, directions for use, and inactive ingredients as a series of short sentences or single words separated by bullet points. The Drug Facts template is a much more concise document than the QRD template 9 and is more a short list of details about the medicine. The sections contained are the same as in the QRD template 9 although directions for use are located at the end of the label rather than in section 3 as in the QRD template.

A comparison of the content and order of the information in these three documents used in the United States with QRD template 9 is shown in table 18. All patient information templates start with the name of the product and active ingredient. The basic content of the patient information in the United States is similar in all documents to that of the European QRD template 9 but varies in how much detail is provided for the user. The order of information contained is most similar between the MedGuide and the QRD template 9. Whereas the medication guide provides a series of questions as headings, the others all use brief statements pertaining to the contents of the section as in the QRD template 9. Use of standard or fixed statements is not commonly seen in the United States and only one verbatim statement that 'Medicines are sometimes prescribed for purposes other than those listed in a medication guide' is defined in the legislation for MedGuides. Only common side effects are usually described without a definition of frequency. A number of standard warning statements are defined for OTC medicines such as 'allergy alert' or 'choking' for gums. The CMI is the only US document to describe to patients how to monitor themselves for an improvement in their condition. This is not reflected in the QRD template 9.

Table 18: Comparison of the content and order of information contained in the Medication Guide, CMI, labelling of OTC medicines and the QRD template 9

Medication Guide[163]	**CMI**[159]	**OTC medicines**[154] **- Drug facts**	**QRD template 9**[48]
Brand name and phonetic spelling	Drug names, approved uses, and what to watch for to see if you are getting better	Active ingredient	{(Invented) name strength pharmaceutical form} {Active substance(s)}
What is the most important information I should know about (name of drug)?	Contraindications	Purpose (general pharmacological category)	What X is and what it is used for
What is (name of drug)?	How to use and store the medicine and what to do in case of overdose	Uses	
Who should not take (name of drug)?	Specific warnings and things to watch for about the medicine	Warnings	What you need to know before you <take> <use> X (Section for contraindications, warnings and precautions)
How should I take (name of drug)?	Symptoms of serious or frequent adverse reactions and what to do	Do not use	How to <take> <use> X
What should I avoid while taking (name of drug)?	General information such as when to talk to doctor	Ask a doctor before use if you have	
What are the possible or reasonably likely side effects of (name of drug)?		When using this product	Possible side effects
Name and place of business of the		Stop use and ask a doctor if	How to store X

Medication Guide[163]	CMI[159]	OTC medicines[154] - Drug facts	QRD template 9[48]
manufacturer, packer, or distributor			
The date of the most recent revision of the medication guide		Directions	Contents of the pack and other information This leaflet was last revised in <{MM/YYYY}> <{month YYYY}>.
		Other information	
		Inactive ingredients	
		Questions	

4.5 Comparison of QRD template 9 to other templates published by non-EU countries

The use of a template for the package leaflet provides advantages as a standard format and set order make it easier for the user to locate particular information as the information provided with all medicines information is identical in structure. The order and content of information contained in the template for the package leaflet from Switzerland, templates for Consumer Medicine Information in Australia and New Zealand, United States Medication Guides and in the European QRD template 9 is surprisingly similar as shown in table 19. The Swiss template and QRD template are the only documents in the comparison which use numbered sections and an information box at the start of the leaflet. The Swiss template shows the most detailed subdivision of information with the greatest number of section headings of any of the compared templates. A contents list is only seen in the QRD template. CMI from Australia and New Zealand should also however use numbered sections and a contents table when the leaflet is longer than 4 pages. The Swiss template uses questions as title headings while all others all use brief sentences relating to the content of the section. In general all templates start with what the medicine is used for, followed by contraindications, warnings and precautions, how to use the medicine and side effects. Information such as a description of the product, manufacturer, marketing authorisation holder and date of approval of the leaflet are located in all templates near the end of the template. The QRD template 9 and those for the CMI in Australia and New Zealand allow for a description of the benefits of using the medicine. Self-help methods to improve the present health condition are allowed for in Australia, New Zealand and Switzerland. Whether a product is addictive and use of phonetic spellings are also seen in the CMI template in Australia and New Zealand. Whereas a subheading in QRD template 9 is present for declaration of excipients defined in the Excipients Guideline[94], excipients to which a patient might react to are only described on the labelling of the product in Australia and New Zealand. The Swiss template only makes allowance for declaration of allergy to food preservatives or dyes.

Table 19: Comparison of QRD template 9 to templates from Switzerland, Australia, New Zealand and the USA

Swiss template[129]	QRD template 9[48]	CMI Australia[143]	CMI New Zealand[152]	US Medication Guide[163]
Section heading/Subheading				
1. Information für Patientinnen und Patienten* (Information for patients)	{(Invented) name strength pharmaceutical form} {Active substance(s)} Information box prescription/OTC medicines and index 'What is in this leaflet'	**What is in this leaflet**	**What is in this leaflet**	Brand name and phonetic spelling
2 (a) Name des Präparates* (Name of the product)				**What is the most important information I should know about (name of drug)?**
***3.* Was ist … und wann wird es angewendet?** (What is …. and what it is used for)	**1. What X is and what it is used for**	**What [Medicine name] is used for**	**What [Trade name] is used for**	**What is (name of drug)?**
4. Was sollte dazu beachtet werden? (What else should be taken into consideration?)	**2. What you need to know before you <take> <use> X** Do not <take> <use> X<:> Warnings and precautions Children <and adolescents> Other medicines and X X with <food> <and> <,> <drink> <and> <alcohol>	**Before you take/use/have/are given [Medicine name]** When you must not take it Before you start to take it Taking other medicines	**Before you use [Trade name]** When you must not use it Before you start to use it Taking other medicines	**Who should not take (name of drug)?**
5. Wann darf …. nicht eingenommen/angewendet werden? (When should … not be taken/used?)				
6. Wann ist bei der				

Swiss template[129]	QRD template 9[48]	CMI Australia[143]	CMI New Zealand[152]	US Medication Guide[163]
Section heading/Subheading				
Einnahme/Anwendung von … Vorsicht geboten? (When should care be taken during use of …?) **7. Darf … während einer Schwangerschaft oder in der Stillzeit eingenommen/angewendet werden?** (Can … be used during pregnancy or breast-feeding?)	Pregnancy <and> <,> breast-feeding <and fertility> Driving and using machines <X contains {name the excipient(s)}>			
8. Wie verwenden Sie …? (How should you use …?)	**3. How to <take> <use> X** <Use in children <and adolescents>> <If you <take> <use> more X than you should> <If you forget to <take> <use> X> <If you stop <taking> <using> X>	**How to take [Medicine name]** How much to take How to take it When to take it How long to take it If you forget to take it If you take too much (overdose)	**How to use [Trade name]** How much to take When to take it How long to take it If you forget to take it	**How should I take (name of drug)?**

Swiss template[129]	QRD template 9[48]	CMI Australia[143]	CMI New Zealand[152]	US Medication Guide[163]
Section heading/Subheading				
		While you are using [Medicine name] Things you must do Things you must not do Things to be careful of Things that would be helpful for ……	**While you are using [Trade name]** Things you must do Things you must not do Things to be careful of **In case of overdose** If you take too much (overdose)	**What should I avoid while taking (name of drug)?**
9. Welche Nebenwirkungen kann … haben? (Which side effects can … have?)	**4. Possible side effects <Additional side effects in children <and adolescents>> Reporting of side effects**	**Side effects**	**Side effects**	**What are the possible or reasonably likely side effects of (name of drug)?**
10. Was ist ferner zu beachten? (What else should be taken into consideration?)	**5. How to store X**	**After using [Medicine name]** Storage Disposal	**After using [Trade name]** Storage Disposal	
11. Was ist in … enthalten? (What is contained in …?)	**6. Contents of the pack and other information**	**Product description** What it looks like	**Product description** What it looks like	

Swiss template[129]	QRD template 9[48]	CMI Australia[143]	CMI New Zealand[152]	US Medication Guide[163]
Section heading/Subheading				
12. Zulassungsnummer (Marketing authorisation number)	What X contains What X looks like and contents of the pack Marketing Authorisation Holder and Manufacturer	Ingredients Manufacturer/Distributor/ Supplier	Ingredients Manufacturer/Distributor/Supplier	**Name and place of business of the manufacturer, packer, or distributor**
13. Wo erhalten Sie …? Welche Packungen sind erhältlich? (Where can you get ….? Which packets are available?)			**Sponsor details**	
14. Zulassungsinhaberin (Marketing authorisation holder)				
15. Herstellerin (manufacturer)				
16. Diese Packungsbeilage wurde im… (Monat/Jahr) letztmals durch die Arzneibehörde (Swissmedic) geprüft. (This package leaflet was last reviewed by the Drug administration authority (Swissmedic) in….)	This leaflet was last revised in <{MM/YYYY}> <{month YYYY}>.		**Date of preparation**	**The date of the most recent revision of the Medication Guide**

4.6 Analysis of QRD template implementation in package leaflets of centralised approved medicines

On the evening of 21.10.2011 to 23.10.2011, package leaflets in the English language of centralised approved human medicines were downloaded from the EMA website. Of the 616 package leaflets which were downloaded it was possible to analyse 565. The other 51 could either not be converted into Word documents, large passages of text remained as pictures or caused the Microsoft Office Word 2007 program to continually crash. Authorisation dates for the analysable medicines ranged from 20.10.1995 to 03.10.2011 and the number of revisions of the documentation was up to 38 times.

The second download took place on 03.10.2012. Of the 565 package leaflets which were analysable in the first download, 423 had been updated at the time of the second download (74.9 %). The authorisation for none of these medicines had been either suspended or withdrawn. The 423 package leaflets were therefore downloaded from the EMA website to be analysed and compared to the leaflets in the first download. Leaflets from the first download which had not been altered since this date were integrated into the data set for analysis.

The third download took place on 07.10.2013. Of the 565 package leaflets which were analysed in the first and second download, 411 had been updated since the second download (72.7 %), 118 had not been updated (20.9 %), 34 products had been withdrawn and 2 had been suspended (6.4 %). The package leaflets for these 36 withdrawn or suspended medicines were therefore subsequently removed from the data set used for analysis as they had not been developed further. The 411 updated leaflets were downloaded from the EMA website to be analysed and compared to the leaflets in the first and second downloads. Leaflets from the first and second downloads which had not been altered were again integrated into the data set for analysis.

4.6.1 Types of medicines registered using the centralised authorisation procedure at the EMA

Most of the medicines of the analysed package leaflets in the first download were available only on prescription (98.9 %) while six were available over-the-counter. The types of medicine were also sorted into pharmaceutical forms. The most common type according to pharmaceutical form noted in the package leaflets were products for parenteral administration (injections and infusions) and film-coated tablets (table 20).

The calculation of the 95 % confidence interval showed that the percentage of package leaflets in the initial sample of 616 documents always fell between the upper and lower limits of the confidence interval range for all groups within each three of the defined categories (tables 20 and 21). It can therefore be

concluded that the analysed sample of 565 package leaflets is representative of the initial sample of 616 package leaflets and thereby consequently representative of the package leaflets for all centralised approved human medicines on the EMA website.

Table 20: Distribution of the analysed 565 package leaflets according to prescription status and pharmaceutical form of the medicines in the first package leaflet download from the EMA website including the complete sample of 616 package leaflets

Assessed component	Sample of 565 package leaflets			Initial sample of 616 package leaflets (%)
	n	%	95 % confidence interval	
Sales status				
Prescription only	559	98.9	98.1 – 99.8	99.0
OTC	6	1.1	0.2 – 1.9	1.0
Pharmaceutical form				
Film-coated tablets	152	26.9	23.2 – 30.6	27.9
Parenteral administration forms	209	37.0	33.0 - 41.0	37.5
All other tablets including dispersible, buccal, prolonged release	79	14.0	11.1 – 16.8	12.8
All capsules including soft, hard, gastro-resistant	61	10.8	8.2 – 13.4	11.2
Others (e.g. nasal spray, eye drops, transdermal plasters)	64	11.3	8.7 – 13.9	10.6

When examining the first letter of the ATC code of the medicines in the first download, the most commonly represented anatomical group was antineoplastic and immunomodulating agents (ATC code starting with L) followed by antiinfectives for systemic use (ATC code starting with J) (table 21).

Table 21: Percentage of package leaflets in the first download which were analysed, and the complete sample of 616 package leaflets downloaded from the EMA website, relating to the anatomical main group of medicines according to ATC code

First letter of ATC code	Drug classification	Sample of 565 package leaflets			Initial sample of 616 package leaflets (%)
		n	%	95 % confidence interval	
A	Alimentary tract and metabolism	72	12.7	10.0 – 15.5	12.0
B	Blood and blood forming organs	60	10.6	8.1 – 13.2	10.9
C	Cardiovascular system	50	8.8	6.5 – 11.2	8.4
D	Dermatologicals	5	0.9	0.1 – 1.7	0.8
G	Genito-urinary system and sex hormones	30	5.3	3.5 – 7.2	5.4
H	Systemic hormonal preparations, excluding sex hormones and insulins	11	1.9	0.8 – 3.1	1.8
J	Antiinfectives for systemic use	90	15.9	12.9 – 18.9	16.2
L	Antineoplastic and immunomodulating agents	111	19.6	16.4 – 22.9	19.6
M	Musculo-skeletal system	21	3.7	2.2 – 5.3	3.7
N	Nervous system	68	12.1	9.4 – 14.7	12.7
R	Respiratory system	13	2.3	1.1 – 3.5	2.1
S	Sensory system	10	1.9	0.7 – 2.9	2.3
V	Various (e.g. radiopharmaceuticals for diagnosis, iron chelators)	24	4.3	2.6 – 5-9	4.1

4.6.2 Use of the contents list and sentences contained in the information box at the start of the QRD template for the package leaflet

All package leaflets in the first download were determined to have used QRD template 7. Although there are 5 different subversions of QRD template edition 7, none of the minor changes existing between these template versions affected the elements which were analysed in this study, meaning that a further subdivision of package leaflets with QRD template 7 into sub-editions of this template version was not carried out.

Six of the 565 examined contents lists in the first download were not completely QRD template conformal as instead of the standard 6 sections, section 4, for example, was used for information for diabetics. Consequently the information normally included in sections 4, 5 and 6 was moved into sections 5, 6 and an additional section 7. In four other cases, point 7 was also included in the contents list for further information or patient instructions.

Two package leaflets in all three downloads contained subheadings in the contents list which increased the number of words for the standard contents list from approximately 36 to 161 words in one case and in the other to 149 words. In all downloads, six of the examined leaflets did not contain a contents list but due to other aspects of template wording present in the package leaflets, these were designated to have used QRD template 7 (table 22). In the second download, 183 of the 559 leaflets with a contents list, contained the contents list according to QRD template 8. In the third download, 278 of the 523 leaflets with a contents list contained the list which was first described in QRD template 8, and a further 81 package leaflets had the new paragraph from QRD template version 9 regarding the reporting of side effects to the national authorities. Of these 81 leaflets, 21 had the black symbol for 'additional monitoring' resulting from Directive 84/2010/EU[42]. A cross-reference to 'see section 4' is included in the information box from QRD template 9 to aid patients in locating potential side effects. In the third download, 59 leaflets from the 529 studied had a reference to section 4 in the information box (4 with QRD template 8 in the absence of the new section for reporting side effects, and 55 with QRD template 9).

Table 22: Package leaflets downloaded from the EMA website assessed relating to the presence of contents list, inclusion of section 'Reporting side effects' and points in the information box of the QRD template

Aspect contained in the package leaflet	**Percentage package leaflets with the wording provided in the left column** (%)		
	Download 1 (n = 565)	**Download 2 (n = 565)**	**Download 3 (n =529)**
Contents list	99.0	99.0	98.9
Package leaflets using QRD template 7	100	67.6	32.1
Package leaflets using QRD template 8	0	32.4	52.6
Package leaflets with QRD template 9 section 'Reporting side effects'	0	0	15.3
Info box point 1	100	100	100
Info box point 2	100	100	100
Info box point 3	85.0	82.7	82.4
Info box point 4	100	100	100

The information box was present in all package leaflets although not always template conformal. In the first download, seven package leaflets included extra information, for example, regarding patient alert cards and in one case the patient was told to refer to the SmPC as the package leaflet did not contain all the information about the medicine. Points 1, 2 and 4 were always present in all downloads, whereas point 3 was absent in 15.0 to 17.6 % of the leaflets (table 22). Point 3 contains the information for prescription only medicines that 'This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours'[48,49,51]. This point is in pointed brackets in template versions 7, 8 and 9 meaning that it can be omitted. Where it was absent, the fact that the patients may never handle the medicine themselves had been taken into consideration, which is reflected by the type of product (table 23). Some products which are injected can be administered by the patient after appropriate instructions from a doctor or healthcare professional. Leaflets for these medicines usually contained patient information on 'how to inject yourself' at the end of the leaflet or detailed instructions in section 3 'How to take X'[48,49,51].

Table 23: Percentage of package leaflets downloaded from the EMA website according to medicine type where point 3 in the information box of the QRD template had been omitted

Type of medicine	**Percentage of package leaflets according to type of medicine** (%)		
	Download 1 (n = 85)	**Download 2 (n = 98)**	**Download 3 (n = 93)**
Parenteral administration forms	81.2	82.6	85.9
Radiopharmaceuticals	4.7	4.1	3.2
Others (e.g. capsules, medicated sponge, inhalation gas, sealant)	14.1	13.3	10.9

QRD template 7 offers the choice of the words 'doctor' and/or 'pharmacist' in point 2 of the information box at the beginning of the package leaflet which was extended to include 'nurse' from QRD template 8. Point 2 of the information box was therefore further analysed to see which terms were preferred (table 24).

Table 24: Percentage of package leaflets downloaded from the EMA website assessed according to terms used in point 2 of the information box of the QRD template

Terms used in point 2: If you have any questions ask your...	**Percentage package leaflets with the wording provided in the left column** (%)		
	Download 1 (n = 565)	**Download 2 (n = 565)**	**Download 3 (n = 529)**
Doctor or pharmacist	82.3	71.9	64.7
Doctor	8.6	8.7	7.9
Doctor, pharmacist or nurse/healthcare professional	5.1	15.2	23.4
Doctor or nurse	1.5	2.1	3.0
Other (e.g. nuclear medicine specialist, anaesthetist, midwife, doctor or healthcare professional)	2.3	2.1	0.9

Use of the terms ‘doctor or pharmacist’ was most common. Use solely of the term ‘doctor’ or additional names such as ‘surgeon’ or ‘anaesthetist’ reflected the nature of the product. In the second and third downloads, use of the three terms ‘doctor, pharmacist or nurse/healthcare professional’ greatly increased.

4.6.3 Number of words caused by the QRD template, the list of local representatives of the marketing authorisation holder, additional information for patients and health professionals

The number of words in each package leaflet from each download were counted. Although only a few package leaflets were available with last approval date between 2007 and 2009, the general trend shows that the total number of words and the number of words caused by the QRD template had increased up to the present day in the patient information (table 25).

The total number of words in the examined leaflets from the first download ranged from 799 to 6249, 808 to 7776 in download 2 and 1078 to 7822 in the third download. In the QRD template, X should be replaced by the medicine name which means that a long product name could influence the word count. In no cases were the pharmaceutical form and dosage strength written throughout the leaflet, but found only at the top of the package leaflet. Most product names consisted of one or two words. For two vaccines in the three downloads, however, the product names contained 5 and 10 words respectively. In the case that a 10 word product name is included the maximum of 24 times in a leaflet written according to QRD template version 7, the number of words is increased by 216 in comparison to a one word name. Through the use of the term ‘this medicine’ in QRD templates 8 and 9, the number of times the product name is mentioned is reduced to a maximum of 19. Product names used outside the QRD template text are not considered in the found numbers.

Although the QRD template states at the end of the leaflet after section 6 ‘The following information is intended for healthcare professionals only:’ in some cases, this section also contained information for patients which contributed to a large extent in the amount of the total text. Three package leaflets in the first download, one in the second download and seven in the third download contained information both for the patient and healthcare professionals. Information for patients on how to administer the medicine themselves or ways of improving their condition, and for healthcare professionals on how to give the medicine or store it accounted for up to 64.7 % and 50.5 % respectively of the total words in the first download, 66.8 % and 51.9 % in the second download and 67.3 % and 53.7 % in the third download (table 26). In the case where only 0.8 % of the text of the leaflet contained information for healthcare professionals, the doctor was simply told to refer to the SmPC.

Table 25: Date of last update of the product information and average number of total words and QRD template plates contained in the package leaflets of centralised approved medicines downloaded from the EMA website

No. of leaflets	Year of last update	Percentage of products (%)	Average no. total words	Average no. total words per download	Average no. QRD template words*	Average no. QRD template words* per download
Download 1 (n = 565)	2007	0.9	1886	2436	372	444
	2008	0.5	2485		402	
	2009	4.2	1984		431	
	2010	13.7	2229		444	
	2011 (up to 21.10.2011)	80.7	2501		446	
Download 2 (n = 565)	2007	0.6	1674	2576	389	468
	2008	0	-		-	
	2009	1.6	1838		389	
	2010	3.7	2226		443	
	2011	24.2	2561		453	
	2012 (up to 03.10.2012)	69.9	2574		477	
Download 3 (n = 529)	2007	0.2	1347	2638	314	499
	2008	0	-		-	
	2009	0.6	1774		372	
	2010	0.8	2127		423	
	2011	4.9	2380		465	
	2012	22.5	2636		473	
	2013 (up to 07.10.2013)	71.0	2672		511	

* The number of words from the list of MAH representatives was not included in this analysis

Table 26: Analysis of the number of words contained in package leaflets downloaded from the EMA website with regard to additional patient text, information for healthcare professionals, QRD template text for each template version and the address list for representatives of the marketing authorisation holder

Aspect contained in the package leaflet	Download	Leaflets with text (%)	Minimum words	Maximum words	Average words	Percentage (%) of total words
Additional Patient information text	**1**	10.6	56	2569	955	3.0 - 64.7
	2	9.7	53	5192	883	2.8 - 66.8
	3	11.7	56	5264	938	2.7 - 67.3
Healthcare professional information	**1**	24.4	12	1982	416	0.8 - 50.5
	2	23.9	12	2107	455	0.8 - 51.9
	3	24.6	12	2155	429	0.6 - 53.7
Words caused by QRD template* (without list of MAH representatives)	**1 - QRD template 7 (n = 565)**	100	256	596	444	6.7 - 39.4 (average 19.7)
	2 - QRD template 7 (n = 382)	67.6	286	623	450	6.4 - 39.9 (average 19.6)
	2 - QRD template 8 (n = 183)	32.4	289	627	509	7.2 - 34.1 (average 20.5)
	3 - QRD template 7 (n = 170)	32.1	314	591	451	6.7 - 39.0 (average 20.0)
	3 - QRD template 8 (n = 278)	52.6	289	610	509	7.2 - 38.2 (average 20.3)
	3 - QRD template 9 (n = 81)	15.3	408	643	565	11.9 - 34.8 (average 21.5)
List of MAH representatives	**1**	82.3	18	559	249	1.0 - 33.3 (average 13.0)
	2	84.2	18	637	311	0.6 - 31.2 (average 12.8)
	3	85.8	19	639	311	0.6 - 33.6 (average 12.4)

* Leaflets without a contents list were designated to have used QRD template 7

The number of words caused by the text printed in the QRD template in black of the first download ranged from 256 to 596 (average 444, table 26). This accounted here for up to 39.4 % of the total text. In the second and third downloads, the number of words in each package leaflet caused by the QRD template was analysed according to whether the leaflet used QRD template version 7, 8 or 9. The average number of words caused by the templates had increased with increasing version number. The volume of text increase was approximately by 10 % between leaflet versions. However, the maximum percent of the total words caused by the templates decreased in the second and third downloads when comparing the leaflets with template 7 and 8 in the second download and template 8 and 9 in the third download, even though the maximum QRD template words had increased. The minimum number of words caused by QRD template 9 is increased by 119 words in comparison to leaflets with QRD template 8.
QRD template 7 contains approximately 640 words (depending on subversion number) while QRD template 8 contains a maximum of 771 words (see section 4.1.1) and QRD template 9, 840 words. From the first download, leaflets therefore used a maximum of 69 % of the QRD template 7 text. In the second download leaflets with QRD template 8 used a maximum of 66 % of the provided text. In the third download leaflets with QRD template 9 used a maximum of 67 % of the template text.

4.6.4 Reference in section 2 to section 6 for location of the list of other ingredients

In section 2 of the package leaflet for QRD template version 7, patients were told not to take the medicine if they were 'allergic (hypersensitive) to the active ingredient or any of the other ingredients'[51]. QRD templates 8 and 9 now tell the patient where to find the list of other ingredients, namely in section 6. Although all examined leaflets in the first download were QRD template version 7 according to the wording of the contents list, many already included a reference to section 6. Wording here varied between leaflets but in many cases the patient was told directly to refer to section 6, or alternatively 'the list of ingredients contained at the end of the leaflet'. 39.1 % of the leaflets contained a reference in some form as to where to find the excipients. In the second download, 56.4 % of the 565 leaflets contained a reference to section 6 regardless of whether QRD template 7 or 8 had been used and in the third download, 74.1 % had a reference. However, a subanalysis of the leaflets in the second download with QRD template 8 showed that 10.9 % of these had no reference to section 6 and 6.3 % in the third download of the leaflets with QRD templates 8 or 9.

4.6.5 Method of presenting the frequency of side effects

No specific structure for the side effect section of the package leaflet was recommended in QRD template 7. This was updated from version 8 where a clear organisation of the information is recommended whereby the most serious side effects should be listed first with instructions for what action the patient should take. This was first suggested in the sample package leaflet contained in the Readability Guideline

from 1998[36] and again in the revised version in 2009[38] in the 'Recommendations for the package leaflet' section. Table 27 shows that nearly half the examined package leaflets in the first download listed the most serious side effects first. This had increased to 74.3 % of the package leaflets in the second download which used QRD template 8 and 79.0 % in the third download for package leaflets with QRD template 9. The patient was usually told to stop taking the medicine straight away and contact their doctor immediately.

The use of MedDRA system organ classes is standard in the SmPC but they are not suggested for the package leaflet, although 0.9 % of the examined package leaflets in the first download did use organ systems. The remaining 99.1 % used side effect frequencies to categorise side effects. In download 2 and 3, organ classes were never used in the side effect section of the package leaflet.

Table 27: Analysis of package leaflets downloaded from the EMA website regarding location of severe side effects and form of presentation of side effect frequency explanations

Presentation of side effects	**Percentage package leaflets with the aspect provided in the left column (%)**					
	Download 1 QRD template 7 (n = 565)	**Download 2 QRD template 7 (n = 382)**	**Download 2 QRD template 8 (n = 183)**	**Download 3 QRD template 7 (n = 170)**	**Download 3 QRD template 8 (n= 278)**	**Download 3 QRD template 9 (n = 81)**
Severe side effects listed first	46.4	51.6	74.3	52.9	73.7	79.0
Frequencies in table or list at start of section 4	49.4	51.3	7.7	45.9	10.4	23.5
Frequencies as part of the side effect list	46.9	44.5	90.7	47.6	88.8	74.0
Other form of side effect frequency presentation	3.7	4.2	1.6	6.5	0.8	2.5

A specific convention for the description of side effect frequencies is recommended for the first time in QRD template 8 where it was additionally advised that 'This frequency convention should not appear before the list of side effects as this takes up space and has shown in user testing to be misleading to patients'[56]. The two main methods used were to note frequency explanations in the form of a table at the start of section 4, or present them as part of the side effect list where a particular frequency is noted followed by a record of all side effects in this category. The preferred method for describing frequency in the first download was as a table. In the second and third downloads, most package leaflets with QRD templates 8 and 9 had listed the frequencies as part of the side effect list (table 27).

Table 28: Analysis of the method of description of the frequency of side effects in package leaflets downloaded from the EMA website

Method of frequency description of side effects	**Percentage of package leaflets containing side effect frequency description method in left column (%)**					
	Download 1 QRD template 7 (n = 565)	**Download 2 QRD template 7 (n = 382)**	**Download 2 QRD template 8 (n = 183)**	**Download 3 QRD template 7 (n = 170)**	**Download 3 QRD template 8 (n= 278)**	**Download 3 QRD template 9 (n = 81)**
Common: affects 1 to 10 per 100 users (BfArM recommendation[120]/ EMA report 2007[182])	66.6	65.4	17.4	57.7	16.2	14.8
Common: May occur in up to 1 in 10 users (QRD template 8/9[50,56])	14.8	17.3	76.0	22.9	78.8	79.0
Common: less than 1 per 10 but more than 1 per 100 users (Readability Guideline, 1998[36])	10.5	8.1	3.3	6.5	0.7	0
Other	8.1	9.2	3.3	12.9	4.3	6.2

The majority of package leaflets in the first download used the side effect explanation type ‘common, affects 1 to 10 per 100 users’ (table 28) which is described by BfArM[120] and the EMA[182]. The next most commonly used description type was ‘common: may occur in up to 1 in 10 users’ which is similar to the recommendation of QRD templates 8 and 9 namely ‘Common: may affect up to 1 in 10 people’[50,56]. In the second download, the BfArM/EMA defined description from 2007 of side effects was still used most frequently for package leaflets using QRD template 7, however those using QRD template 8 mostly used the frequency convention described in the annotated version of this template. The third download also showed that package leaflets with QRD template version 8 or 9 most commonly used the recommendation described since publication of QRD template 8 (table 28).

QRD templates 8 and 9 mention in the annotated version that double sided expressions such as 'common, less than 1 per 10 but more than 1 per 100' are not well understood[50,56]. This method of description was used in 10.4 % of examined package leaflets in the first download but decreased in both the second and third downloads regardless of which template version had been used (table 28).

4.6.6 Text headings and standard statements in section 2 of the package leaflet

The first bullet point in section 2 of the package leaflet differs between QRD template 7 and 8/9. In QRD template 7, the patient is told not to take the medicine if they are ‘allergic (hypersensitive)’ to ingredients or excipients in the product whereas in templates 8 and 9, the term ‘allergic’ is used alone. Of the examined leaflets with QRD template 8 in the second download, 79.2 % had only used the term ‘allergic’ according to QRD template 8. In the third download, the percent of leaflets with QRD templates 8 and 9 which only used the term ‘allergic’ was 77.2 %.

The next heading in section 2 is ‘Take special care with X’ in QRD template 7[51] which was changed from template 8 to ‘Warnings and precautions’[48,49]. Of the 183 leaflets in the second download with the template 8 contents list, 92.9 % had used the heading ‘Warnings and precautions’ and of the 359 leaflets in the 3rd download with QRD template 8 or 9, 93.6 %. Interestingly, 3.3 % of the leaflets in the second download had used the headings from both QRD templates 7 and 8 and 1.7 % in the third download. A small percent of package leaflets contained a warning sentence which was neither conform to QRD template 7 nor 8/9.

Under the heading ‘Other medicines and X’, the standard warning statements differ between QRD template 7 and 8/9. In QRD template 7, the patient is told ‘Please tell your <doctor> <or> <pharmacist> if you are <taking> <using> or have recently <taken> <used> any other medicines, including medicines obtained without a prescription’[51] while since QRD template 8, the sentence was altered to ‘<Tell your <doctor> <or> <pharmacist> if you are <taking> <using>, have recently <taken> <used> or might <take>

<use> any other medicines[48,49]. 62.3 % of the leaflets with QRD template 8 contents list in the second download had used the statement from template 8, while 27.9 % had included the sentence from template 7. In the third download, 69.9 % of the leaflets with QRD templates 8 and 9 contents list had the statement from template 8 or 9 while 21.4 % still retained the statement from template 7. The remaining leaflets had a statement which was conform to neither template.

A further heading contained in QRD templates 7, 8 and 9 regards taking the named product with food and drink and additionally the optional term 'with alcohol' since QRD template 8. Table 29 shows how often each term was used in the leaflets which contained a relevant subheading. In a more detailed examination of the leaflets in the second and third downloads where the heading 'food and drink' had been used, 12 % in the second download contained information regarding drinking alcohol with the product, although this wasn't included in the heading, and 9.1 % in the third download. In leaflets where 'food, drink and alcohol' were included, 10.5 % in the second download and 11.1 % in the third download however contained no information regarding alcohol consumption.

Table 29: Analysis of the frequency of use of the terms food, drink and alcohol in the subheading 'Taking X with food, drink and alcohol' in package leaflets downloaded from the EMA website

Subheading: 'Taking X with….'	**Percentage of leaflets using text element shown in left column (%)**	
	Download 2 (n = 81)	**Download 3 (n = 162)**
Food	1.2	0.6
Food and drink	58.1	54.9
Food, drink and alcohol	23.5	22.3
Alcohol	17.3	20.4
Drink	0	0.6
Drink and alcohol	0	1.2

Information for pregnant and breast-feeding women is also included in section 2 under the subheading 'Pregnancy and breast-feeding' in QRD template 7 and additionally the optional term 'fertility' since QRD template 8. The majority of leaflets in the second and third download had only used the terms 'pregnancy and breast-feeding' (72.7 % and 72.1%). The additional term 'fertility' was seen in both the second download in 25.1 % of examined leaflets and 25.3 % in the third, although 58.7 % of these provided no information on fertility in the second round, and 67.8 % in the third round making the term 'fertility' superfluous. The remaining leaflets did not provide this subheading in section 2.

Under the subheading for pregnancy and breast-feeding is an optional standard sentence in QRD templates 7, 8 and 9. The wording differs however between each template version, whereby QRD template 7 states 'Ask your doctor or pharmacist for advice before taking any medicine'[51], QRD templates 8 and 9 advise 'If you are pregnant or breast-feeding, think you might be pregnant or are planning to have a baby, ask your <doctor> <or> <pharmacist> for advice before taking this medicine'[48,49]. Table 30 shows the frequency with which each statement was used for leaflets containing a relevant subheading.

Table 30: Analysis of the pregnancy and breast-feeding advice sentence contained in package leaflets downloaded from the EMA website

Sentence from template version	**Percentage of package leaflets containing pregnancy and breast-feeding advice sentence shown in the left column (%)**	
	Download 2 (n = 183)	**Download 3 (n = 359)**
QRD template 7 conform	20.8	17.0
QRD template 8/9 conform	41.5	44.8
Neither template conform	35.5	35.4
Sentences from QRD templates 7 and 8/9	2.2	2.8

The final sentence in section 2 should be to advise patients on certain excipients in the case that they are contained in the product according to the Excipients guideline[94]. In QRD template 7, the subheading 'Important information about some of the ingredients of X' is used while since QRD template 8, the patient is told 'X contains {name the excipient(s)}'[48,49, 51]. Of the leaflets identified to have used elements from QRD templates 8/9, 60.0 % from download 2 and 63.2 % from the third download contained an excipient which had to be mentioned in the package leaflet. The heading since template 8 was used in the majority of these leaflets in both downloads where an excipient was contained (download 2: 87.7 %, n = 106; download 3: 91.2 %, n = 207).

4.6.7 Presentation of the list of local representatives of the marketing authorisation holder

The list of local representatives of the marketing authorisation holder must not necessarily be included at the end of the package leaflet, but when it is present, addresses must be included for all 29 listed countries (increased to 30 in version 9[48]). Astoundingly, although inclusion of this list greatly increases the length of the leaflet, it was present in 82.3 % to 85.8 % of the investigated package leaflets (table 26) where it accounted for up to 33.6 % of the text. On average the MAH list contributed to approximately 12.4 % to 13.0 % of the text volume when it was present.

QRD templates 7, 8 and 9 recommend a structure for the information regarding the MAH, for example:
United Kingdom
{Name}
<{Address}
{Town} {Postal code} – UK>
Tel: + {Telephone number}
<{e-mail}>
Following the bracketing convention therefore means that name of the MAH representative and telephone number are the minimal information required. An email address is optional and postal address can be added, space permitting. For each package leaflet it was noted which of these elements were present (table 31). In most cases, only the country name and name and telephone number of the local representative was included. Only 2.6 % of the examined leaflets in the first download and third downloads contained the maximum number of address fields and 2.7 % in the second download.

In order to save space, QRD template 7, 8 and 9 suggest listing the local representatives sequentially rather than in a tabulated format. A detailed analysis of the MAH representative lists in the first download showed that only two leaflets contained a sequential list while nine leaflets actually included the information in a table with lines. The guidance in the template also states that ‘where the same representative is designated for more than one country, the representative’s details may be listed only once below the names of the countries concerned’[48,49]. In one case in the first download, the MAH had just included one address in this section and listed no countries, while another had abreviated the country names to just two initials per country. One address was valid in this case for 24 countries which greatly reduced the text volume of this section. Only five leaflets in the first download listed one address under more than one country name.

Table 31: MAH information presented in package leaflets downloaded from the EMA website which contained a MAH representative list

Information present in additional to country name or two letter country code	Percentage of package leaflets downloaded from the EMA website with a MAH representative list and the text elements in the left column (%)		
	Download 1 (n = 465)	Download 2 (n = 476)	Download 3 (n = 454)
Name and telephone number only	70.8	71.4	71.9
Name, address and telephone number	12.3	9.5	7.0
Name, address, telephone number and email address	2.6	2.7	2.6
Name, telephone number and email address	13.8	15.3	16.5
No clear system (mixture of names, addresses, telephone number and emails)	0.7	1.0	2.0

4.7 Readability test of the QRD template version 8, its predecessor and a model template

4.7.1 Results of the pilot readability test

Eight people took part in the pilot round of the readability test whereby four people read the short version of the package leaflets and four people the long BfArM version. Table 32 provides an overview of the demographic data of the participants involved in the pilot readability test.

Table 32: Demographic data of the participants who took part in the pilot readability test

Participant No.	Age	Gender	Education level	Native language	Medicines taken per day	Leaflet version read
1	33	female	university	German	1	short German
2	30	male	university	English	0	short German
3	65	male	university	English	2	short English
4	64	female	10th class	English	0	short English
5	39	male	university	German	0	long BfArM German
6	32	female	university	German	0	long BfArM German
7	58	female	university	German	5 - 7	long BfArM German
8	39	male	university	German	0	long BfArM German

The analysis of the questionnaires returned from the pilot test showed that as some of the wording differs in the package leaflets based on the BfArM sample text as compared to the short text version, that alternative answers could be considered as correct for certain questions. This was the case for questions 5 and 25 regarding the starting dose and breast-feeding respectively. The starting dose was given in milligrams enalapril for package leaflets based on the BfArM sample text and in amount of tablets for short texts. This question tests the comprehensibility of medicine specific information rather than the template and both answers were therefore considered correct. The BfArM sample text allows Enal to be used when feeding older nurslings while the short text contraindicates the use during breast-feeding. Here, both answers were therefore also considered correct depending on the leaflet which had been read. In the pilot test, the question 'What should you do if you notice the side effect 'liver inflammation'? was included in the pilot test. This had caused confusion in many participants as liver problems are mentioned in the side effect section and also elsewhere in each package leaflet. The requested side effect was therefore changed to 'runny nose' as this was only provided in the side effect section.

4.7.2 Description of the demographic data of involved participants

In Germany, 194 people were initially given a package leaflet and questionnaire to complete, of which 177 were returned in the first round of the readability test (return rate 91.2%). Five participants had to be subsequently excluded from the data set of the first test round as they were chemists, nurses or a pharmacy assistant which resulted in a total of 172 people taking part in the first round of the readability test in Germany. In the second round of the readability test, 171 people took part of those in the first round, and 167 in the third round. In England, 83 people were initially given a package leaflet and questionnaire to fill in. 69 people returned the completed questionnaire in the first round of the readability test (83.1 % return rate), 65 in the second round and 63 in the third round.

Table 33: Age range of the participants at the time of the first round of the readability test

Age range (years)	**Percentage of participants with the age range shown in the left column (%)**		
	England short package leaflet (n = 69)	**Germany short package leaflet (n = 76)**	**Germany long BfArM package leaflet (n = 96)**
≤ 19	0	6.6	36.5
≥ 20 - ≤ 39	32.3	27.6	13.5
≥ 40 - ≤ 59	17.6	59.2	42.7
≥ 60 years and older	50.0	6.6	7.3

At the time of the first round of the readability test, the age of the participants in Germany ranged between 16 and 78 for the short text version (average age 42.2 years) and between 14 and 79 for the BfArM text version (average age 36.4 years). In England the age of the participants ranged from 24 to 79 (average age 52 years) (table 33). More females than males took part in the test in both countries (Germany short text version: 57.9 % females, Germany BfArM text version: 61.5 % females; England: 64.7 % females). In Germany 26.2 % of the participants lived in Lichtenfels and 53.1 % in the surrounding area (postcode 96***). In England, participants place of residence were more widely spread. The highest number lived in the Cambridge region (49.3 %, n = 34), while most of the remaining came from the Norwich, Hereford or Manchester areas.

All levels of education were represented in both subject groups (table 34), although in England participants with a university degree were clearly in the majority (66.8 %). The most common 'last practiced occupation' was school child (22.1 %, n = 38) and teacher (n = 16, 9.3 %) in Germany and teacher in England (13.2 %, n = 9). The average number of university years attended of participants with this education level in England was 3.8 and in Germany 4.6.

Table 34: Education level of the participants involved in the readability test

Education level	**Percentage of participants with the education level shown in the left column (%)**		
	England short package leaflet (n = 69)	**Germany short package leaflet (n = 76)**	**Germany long BfArM package leaflet (n = 96)**
8th class	0	9.2	43.7
10th class	7.2	35.5	12.5
A-levels	10.1	11.8	10.4
Polytechnic college	7.2	5.3	8.3
University	66.8	14.5	18.8
Other	8.7	23.7	6.3

The majority of participants took no medication during the first readability test round in both countries (table 35), although in England more medication was used probably as the participants involved were older than those in Germany. When examining the types of medicine taken of the participants who had read the short package leaflet versions, 10 of the 76 people (13.2 %) in

Germany used a medicine to treat high blood pressure and 12 of the 69 participants (17.4 %) in England. Of the 96 participants who had read the long BfArM version of the package leaflet in Germany, 18 took a medicine to treat high blood pressure (18.8 %).

Table 35: Number of medicines taken by day by participants at the time of the first round of the readability test

Medicines used per day	**Percentage of participants who took the number of medicines shown in the left column (%)**		
	England short package leaflet (n = 69)	**Germany short package leaflet (n = 76)**	**Germany long BfArM package leaflet (n = 96)**
0	39.1	65.7	59.4
1	31.9	22.4	25.0
2	17.4	5.3	8.3
3 - 4	7.3	5.3	6.3
5 - 7	2.9	1.3	0
8 - 10	1.4	0	1.0

Table 36: How long participants read a day, and read, heard or saw medical reports in an average week at the time of the first readability test round

How long participants read a day (percentage of participants (%))			
Hours	**England short package leaflet (n = 69)**	**Germany short package leaflet (n = 76)**	**Germany long BfArM package leaflet (n = 96)**
0 - < 1	7.2	30.3	34.4
≥ 1 - < 2	43.5	55.3	36.5
≥ 2 - < 3	33.3	11.8	20.8
≥ 3	15.9	2.6	8.3
In an average week, how long participants read, heard or saw medical reports (percentage of participants (%))			
0 - < 1	50.7	53.9	67.7
≥ 1 - < 2	36.2	27.6	19.8
≥ 2 - < 3	4.3	13.2	10.4
≥ 3	8.7	5.3	2.1

The majority of participants in the readability test in both countries read between 1 and 2 hours a day (table 36). Over 50% read, heard or saw medical reports for up to 1 hour per week.

4.7.3 Analysis of the time taken to answer, locatability and comprehensibility of 26 requested contents

Participants who had read leaflets with QRD template 7.3.1 needed the longest time to answer the questions for all text versions regardless of country and text length (table 37). There was no significant difference in the time needed to complete the questions in Germany or England for the short text versions. However, a significant difference was found for the longer text versions in Germany between the model template and QRD template 7.3.1 ($p = 0.008$) and the model template and QRD template 8 ($p = 0.003$).

Table 37: Time in minutes taken by the participants to answer 26 content questions and number of words contained in each package leaflet

Package leaflet	No. words	Time to answer the 26 content questions (minutes)			
		Calculated median	min.	max.	n
EN-Model-template-short text	1221	17.8	7	35	66
EN-QRD-template-7.3.1-short text	2169	19.7	9	50	62
EN-QRD-template-8-short text	2227	19.3	10	40	64
DE-Model-template-short text	1007	20.7	10	60	71
DE-QRD-template-7.3.1-short text	2002	23.4	10	60	69
DE-QRD-template-8-short text	2023	20.3	10	60	70
DE-Model-template-BfArM text	2893	24.5	5	70	92
DE-QRD-template-7.3.1-BfArM text	3890	29.2	6	90	90
DE-QRD-template-8-BfArM text	3956	28.6	10	120	93

EN = English, DE = German, n = number of participants, min. = minimum, max. = maximum. Some people forgot to note the starting and finishing time to answer the 26 content questions. Therefore 'n' of the locatability time is lower than the 'n' for the correct, wrong and not found answers.

Participants provided the highest percent of correct answers for the short text versions with the model template, followed by QRD template 8 in both countries (table 38). There were significant differences found for the number of correct answers provided between each leaflet version in a group ($p \leq 0.026$) except for the long BfArM text version between the model template and QRD template 8 (appendix 13).

The most wrong answers were provided when package leaflets with QRD template 7.3.1 had been read. This result was not affected either by language or the length of the leaflet. There were significant differences found between all leaflet versions for the number of wrong answers provided ($p \leq 0.001$). In Germany, participants gave significantly more not found answers with the model template in comparison to QRD template version 7.3.1 for short package leaflet versions ($p = 0.006$). For the long package leaflet versions there were significant differences in the number of not found answers between the model template and both QRD templates ($p < 0.001$, appendix 13).

Table 38: Calculated median percentage and minimum (min.) and maximum (max.) percentage of correct, wrong and not found answers itemised for each package leaflet

Package leaflet	Percentage correct answers (%)			Percentage wrong answers (%)			Percentage not found answers (%)			n
	Calculated median	min.	max.	Calculated median	min.	max.	Calculated median	min.	max.	
EN-Model-template-short text	95.0	69.0	100	1.3	0	8.0	3.6	0	27.0	67
EN-QRD-template-7.3.1-short text	83.4	69.0	96.0	11.6	0	23.0	3.4	0	27.0	65
EN-QRD-template-8-short text	91.5	73.0	100	5.2	0	15.0	3.0	0	19.0	65
DE-Model-template-short text	93.2	46.2	100	2.2	0	19.2	4.4	0	46.2	75
DE-QRD-template-7.3.1-short text	87.3	50.0	100	9.7	0	26.9	2.7	0	38.5	72
DE-QRD-template-8-short text	91.1	50.0	100	5.0	0	15.4	3.3	0	42.3	73
DE-Model-template-BfArM text	80.4	38.5	96.2	7.7	0	23.1	11.1	0	46.2	93
DE-QRD-template-7.3.1-BfArM text	76.2	34.6	96.2	15.0	3.9	42.3	7.6	0	42.3	93
DE-QRD-template-8-BfArM text	81.2	34.6	100	11.5	0	38.5	6.5	0	38.5	94

EN = English, DE = German, n = number of participants

4.7.4 Analysis of locatability and comprehensibility of QRD template texts intended at the start of the package leaflet

Both QRD template versions 7.3.1 and 8 start with an information box. For the readability test, the active ingredient enalapril had been chosen and therefore the information box for prescription only medicines was investigated. The information that the medicine has been 'prescribed for you', is included in the information box of QRD templates 7.3.1 and 8. This statement was found in section 5 of leaflets using the model template which did not have an information box in order to reduce text volume. It stated there: 'Enal is prescribed only for you'. Participants were asked to identify whether the medicine is available on prescription. Short and long versions of the leaflets with QRD templates 7.3.1 or 8 showed more correct answers than those with the model template although these differences were not significant (table 39). The participants provided significantly more not found answers when using the model template and the German short text version compared to the QRD template 7.3.1 and QRD template 8 ($p \leq 0.035$, appendix 21). For all other leaflet versions, no significant differences were found in the number of wrong or not found answers between the information relating to the prescription status.

Table 39: Percent correct, wrong and not found answers for each package leaflet for the question 'Is this medicine available with or without prescription by a doctor?'

Package leaflet	Is this medicine available with or without prescription by a doctor? (%)			n
	Correct answers	Wrong answers	Not found answers	
EN-Model-template-short text	80.6	1.5	17.9	67
EN-QRD-template-7.3.1-short text	87.7	1.5	10.8	65
EN-QRD-template-8-short text	87.7	4.6	7.7	65
DE-Model-template-short text	65.3	1.3	33.3	75
DE-QRD-template-7.3.1-short text	80.6	5.6	13.9	72
DE-QRD-template-8-short text	76.7	4.1	19.2	73
DE-Model-template-BfArM text	79.6	1.1	19.4	93
DE-QRD-template-7.3.1-BfArM text	82.8	5.4	11.8	93
DE-QRD-template-8-BfArM text	83.0	3.2	13.8	94

EN = English, DE = German, n = number of participants

When a medicine has been prescribed for a patient by a doctor, then it should only be used by them and not given to others, even if it appears that they have similar symptoms. For QRD templates 7.3.1 and 8, the instruction not to pass the prescription medicine on to others is contained in the information box at the start of the leaflet. In the model template, a statement is included regarding this point in section 5. For none of the tested leaflets could a clear disadvantage be identified regarding answering this question and no significant differences between template versions were identified (table 40).

Table 40: Percent correct, wrong and not found answers for each package leaflet for the question 'Should you give Enal to other people to use with a similar illness?'

Package leaflet	Should you give Enal to other people to use with a similar illness? (%)			n
	Correct answers	Wrong answers	Not found answers	
EN-Model-template-short text	97.0	0	3.0	67
EN-QRD-template-7.3.1-short text	98.5	0	1.5	65
EN-QRD-template-8-short text	95.4	0	4.6	65
DE-Model-template-short text	94.7	0	5.3	75
DE-QRD-template-7.3.1-short text	97.2	0	2.8	72
DE-QRD-template-8-short text	97.3	0	2.7	73
DE-Model-template-BfArM text	94.6	1.1	4.3	93
DE-QRD-template-7.3.1-BfArM text	90.3	3.2	6.5	93
DE-QRD-template-8-BfArM text	98.9	0	1.1	94

EN = English, DE = German, n = number of participants

4.7.5 Analysis of comprehensibility and ease of location of information in section 1 of the package leaflet

The indication for a particular medicine was always contained in section 1 of the leaflet regardless of which template had been used. Leaflets with the model template provided the largest percentage of correct answers regardless of whether the text was long or short (table 41). However, this difference was not significant. Also, no significant differences in the number of wrong or not found answers were found between leaflet versions.

Table 41: Percent correct, wrong and not found answers for each package leaflet for the question 'What is Enal used to treat?'

Package leaflet	What is Enal used to treat? (%)			n
	Correct answers	Wrong answers	Not found answers	
EN-Model-template-short text	100	0	0	67
EN-QRD-template-7.3.1-short text	95.4	4.6	0	65
EN-QRD-template-8-short text	100	0	0	65
DE-Model-template-short text	100	0	0	75
DE-QRD-template-7.3.1-short text	95.8	4.2	0	72
DE-QRD-template-8-short text	98.6	1.4	0	73
DE-Model-template-BfArM text	98.9	1.1	0	93
DE-QRD-template-7.3.1-BfArM text	94.6	3.2	2.2	93
DE-QRD-template-8-BfArM text	92.6	7.4	0	94

EN = English, DE = German, n = number of participants

4.7.6 Analysis of comprehensibility and ease of location of information in section 2 of the package leaflet

Section 2 of the package leaflet is the most lengthy and contains a wide range of information ranging from contraindications, interactions, to warnings and precautions. Questions relating to all aspects contained in section 2 were included in the readability test.

Correctly understanding contraindications is of special importance for safe use of any medicine for all users. Women who are pregnant or breast-feeding are a special patient group where it is vital that information can be correctly located as incorrect use could potentially damage the growing foetus, pregnant women or feeding child. Information for pregnant or breast-feeding women was included under a relevant subheading in section 2 of leaflets with QRD templates 7.3.1 and 8. Pregnancy is also a contraindication for the substance enalapril, and was therefore additionally provided in the contraindication section at the start of section 2 in these template versions. The model template used no separate heading/subsection or general sentence as recommended in the QRD template but details are found in the contraindication section. The BfArM text versions provided additional information relating to pregnancy and breast-feeding in the warnings and precautions section of all investigated template versions. Whether pregnant women can use Enal was answered over 96 % correctly for all versions of the

leaflet (table 42). There were no significant differences between template versions for the number of correct answers, wrong answers or not found answers.

Table 42: Percent correct, wrong and not found answers for each package leaflet for the question 'Should women who think they might be pregnant use this medicine?'

Package leaflet	Should women who think they might be pregnant use this medicine? (%)			n
	Correct answers	Wrong answers	Not found answers	
EN-Model-template-short text	98.5	0	1.5	67
EN-QRD-template-7.3.1-short text	96.9	0	3.1	65
EN-QRD-template-8-short text	100	0	0	65
DE-Model-template-short text	98.7	0	1.3	75
DE-QRD-template-7.3.1-short text	98.6	0	1.4	72
DE-QRD-template-8-short text	100	0	0	73
DE-Model-template-BfArM text	100	0	0	93
DE-QRD-template-7.3.1-BfArM text	98.9	0	1.1	93
DE-QRD-template-8-BfArM text	98.9	1.1	0	94

EN = English, DE = German, n = number of participants

The question 'Under what circumstances may breast-feeding women take Enal?' was answered most correctly for the short text versions (table 43). No significant differences were found for the number of correct answers or not found answers between any template versions in either country when using the English or German short package leaflet text.

Use of the BfArM text was shown to cause difficulties in finding and understanding information relating to breast-feeding. This situation which was most pronounced when QRD template 7.3.1 was used although no significant differences were found between template versions for the number of wrong answers.

Table 43: Percent correct, wrong and not found answers for each package leaflet for the question 'Under what circumstances may breast-feeding women take Enal?'

Package leaflet	Under what circumstances may breast-feeding women take Enal? (%)			n
	Correct answers	Wrong answers	Not found answers	
EN-Model-template-short text	95.5	0	4.5	67
EN-QRD-template-7.3.1-short text	100	0	0	65
EN-QRD-template-8-short text	100	0	0	65
DE-Model-template-short text	97.3	0	2.7	75
DE-QRD-template-7.3.1-short text	97.2	0	2.8	72
DE-QRD-template-8-short text	98.6	0	1.4	73
DE-Model-template-BfArM text	87.1	4.3	8.6	93
DE-QRD-template-7.3.1-BfArM text	76.3	10.8	12.9	93
DE-QRD-template-8-BfArM text	87.2	2.1	10.6	94

EN = English, DE = German, n = number of participants

The question 'Can you take this medicine if you are allergic to lactose?' was where the participants provided the fewest correct answers in the readability test (table 44). Whereas QRD template versions 7.3.1 and 8 contain an extra subheading in section 2 stating that the product contains lactose, the model template only lists lactose in the list of ingredients at the end of the leaflet. Many participants understood the wording in the leaflets using the QRD templates 7.3.1 and 8 to mean that they could take Enal providing they had contacted a doctor first and not that they shouldn't if they are allergic to lactose. Although the model template had no extra subheading for lactose, it still produced the largest number of correct answers for the short text leaflet versions in both languages. This difference was significant in England only between the model template and QRD template 8 ($p = 0.015$, appendix 14). No significant difference in correct answers was found between templates for the long or short German text versions.

The question regarding taking the medicine when an allergy to lactose is known, was usually answered more frequently wrongly with leaflets with QRD template 7.3.1 or 8 and 'not found' with leaflets with the model template. The difference was significant in the number of wrong and not found answers between the model template and QRD template 7.3.1 and the model template and QRD template 8 ($p \leq 0.035$) for the short text versions in both countries (appendices 17, 18, 20 and 21). There was also a significant difference

for the long BfArM text in the number of wrong answers between the model template and QRD template 8 ($p < 0.001$, appendix 19), and not found answers between the model template and QRD template 7.3.1 and the model template and QRD template 8 ($p < 0.001$, appendix 23). There was no significant difference in the number of not found or wrong answers between long or short text versions between QRD template 7.3.1 and 8.

Table 44: Percent correct, wrong and not found answers for each package leaflet for the question 'Can you take this medicine if you are allergic to lactose?'

Package leaflet	Can you take this medicine if you are allergic to lactose? (%)			n
	Correct answers	Wrong answers	Not found answers	
EN-Model-template-short text	41.8	10.4	47.8	67
EN-QRD-template-7.3.1-short text	33.8	60.0	6.2	65
EN-QRD-template-8-short text	20.0	75.4	4.6	65
DE-Model-template-short text	38.7	20.0	41.3	75
DE-QRD-template-7.3.1-short text	29.2	61.1	9.7	72
DE-QRD-template-8-short text	30.1	68.5	1.4	73
DE-Model-template-BfArM text	35.5	20.4	44.1	93
DE-QRD-template-7.3.1-BfArM text	36.6	50.5	12.9	93
DE-QRD-template-8-BfArM text	37.2	57.4	5.3	94

EN = English, DE = German, n = number of participants

Section 2 of the tested Enal package leaflet contains warnings and precautions for patients which are applicable under certain situations i.e. when driving and operating machinery or if patients have to undergo an operation. Therefore it was investigated whether users can locate and understand this information. A separate subheading for 'Driving and using machines' was included in section 2 of all template versions. Although most of the participants had located the explanatory statement that 'reaction time may be affected' under the specified subheading, others had read the list of side effects and drawn their own conclusions that adverse effects such as 'tiredness' or 'dizziness' listed in section 4 would also affect the ability to drive and use machines. Common answers provided from leaflets with the BfArM text were that subjects had simply written 'start of treatment' or 'dose increase' which did not answer the question but were explanations contained in the section regarding driving and using machines. In England, 100 % of the subjects could

locate and provide at least one reason why their ability to drive could be affected regardless of the used template version (table 45). No significant differences were found between template versions used in Germany for the long BfArM and short package leaflet texts in the number of correct answers, wrong answers or not found answers.

Table 45: Percent correct, wrong and not found answers for each package leaflet for the question 'Write down one reason why your ability to drive may be reduced due to taking Enal.'

Package leaflet	Write down one reason why your ability to drive may be reduced due to taking Enal. (%)			n
	Correct answers	Wrong answers	Not found answers	
EN-Model-template-short text	100	0	0	67
EN-QRD-template-7.3.1-short text	100	0	0	65
EN-QRD-template-8-short text	100	0	0	65
DE-Model-template-short text	96.0	1.3	2.7	75
DE-QRD-template-7.3.1-short text	98.6	0	1.4	72
DE-QRD-template-8-short text	95.9	0	4.1	73
DE-Model-template-BfArM text	79.6	16.1	4.3	93
DE-QRD-template-7.3.1-BfArM text	76.3	17.2	6.5	93
DE-QRD-template-8-BfArM text	84.0	9.6	6.4	94

EN = English, DE = German, n = number of participants

Warnings and precautions are recommended for the substance enalapril if patients must undergo any operations including those at the dentist. Therefore participants were asked to provide information on what they should do if they have to undergo a dental operation. The most correct answers were provided by participants using the model template independent of language or whether the text version was long or short (table 46). The differences in correct answers provided between the model template and both QRD template versions with short text in England were significant as well as between leaflets with QRD template 7.3.1 and 8 ($p \leq 0.002$, appendix 14). For the short text version in Germany, significant differences in the number of correct answers were found between the model template and QRD template 7.3.1 and QRD template 7.3.1 compared to QRD template 8 only ($p < 0.001$, appendix 15). However, no significant difference in the number of correct answers was found between the templates used with the BfArM text.

Participants who had read the short text version and QRD template 7.3.1 had the greatest problems in correctly answering or locating the information in the short text package leaflets, where this information was presented in a bullet point below the subheading 'Take special care with Enal'. In the longer BfArM text version with template 7.3.1, a sentence was included that the user should inform their dentist before an operation using the same 'Take special care with...' subheading. For QRD template 8, the mandatory statement 'Talk to your doctor, pharmacist or nurse before taking Enal' is presented under the subheading 'Warnings and precautions'. The most common incorrect answer given for package leaflets with QRD template 7.3.1 was that participants had simply answered that 'special care' should be taken if they need dental treatment. This accounted for 93.9 % of the wrong answers in England and 73.1 % in Germany. A significant difference was found for the short text versions between the number of wrong answers provided with the model template compared to leaflets with QRD template 7.3.1 or the leaflets with QRD template 7.3.1 compared to QRD template 8 ($p < 0.001$, appendices 17 and 18). No significant difference in the number of wrong answers was found between the templates used with the BfArM text. A significant difference was only found in the number of not found answers between the model template and QRD template 8 in England ($p = 0.002$, appendix 20) and the short text with the model template and QRD template 7.3.1 in Germany ($p = 0.016$, appendix 21).

Table 46: Percent correct, wrong and not found answers for each package leaflet for the question 'What should you do if you need a dental operation while taking Enal?'

Package leaflet	What should you do if you need a dental operation while taking Enal? (%)			n
	Correct answers	Wrong answers	Not found answers	
EN-Model-template-short text	91.0	0	9.0	67
EN-QRD-template-7.3.1-short text	12.3	70.8	16.9	65
EN-QRD-template-8-short text	72.3	0	27.7	65
DE-Model-template-short text	97.3	1.3	1.3	75
DE-QRD-template-7.3.1-short text	48.6	40.3	11.1	72
DE-QRD-template-8-short text	89.0	2.7	8.2	73
DE-Model-template-BfArM text	88.2	1.1	10.8	93
DE-QRD-template-7.3.1-BfArM text	80.6	3.2	16.1	93
DE-QRD-template-8-BfArM text	81.9	2.1	16.0	94

EN = English, DE = German, n = number of participants

It is of importance that patients inform their doctor if they have just had a kidney transplant before taking the substance enalapril. This precautionary instruction was provided in the short and BfArM package leaflets in a bullet point contained within a list of several other bullet points. To test whether the correct action would be taken by a patient who had had a kidney transplant, a corresponding question was included. Again, the most correct answers were provided by the model template regardless of the length of the package leaflet followed by leaflets with QRD template 8 (table 47). The difference in the number of correct answers provided was significant between the model template and QRD template 7.3.1 and QRD template 7.3.1 and 8 ($p < 0.001$) for all text versions regardless of country and length (appendices 14, 15 and 16). There were no significant differences in the number of correct answers provided between leaflets with the model template and QRD template 8.

Participants who had received leaflets with QRD template 7.3.1 gave more wrong than correct answers. The most common wrong answer provided to this question was again ‘take special care’ without any specific action which accounted for 100 % of the wrong answers in England and 87.5 % in Germany. Significant differences in the number of wrong answers were found for the short text versions between the model template and QRD template 7.3.1 and between leaflets with QRD template 7.3.1 and QRD template 8 ($p < 0.001$, appendices 17 and 18). For the long BfArM text versions, significant differences in the number of wrong answers were found between all template versions ($p \leq 0.031$, appendix 19).

Significant differences in the number of not located answers were identified between the model template and QRD template 7.3.1 and the model template and QRD template 8 in England (both $p = 0.021$, appendix 20). For the long BfArM text versions in Germany, the number of not found answers was significantly different between the model template and QRD template 8 and the QRD template 7.3.1 and QRD template 8 (both $p = 0.035$, appendix 22). No significant differences in the number of not found answers were found between template versions for the short text versions in Germany.

Table 47: Percent correct, wrong and not found answers for each package leaflet for the question 'What should you do if you have just had a kidney transplant and you need Enal?'

Package leaflet	What should you do if you have just had a kidney transplant and you need Enal? (%)			n
	Correct answers	Wrong answers	Not found answers	
EN-Model-template-short text	92.5	6.0	1.5	67
EN-QRD-template-7.3.1-short text	10.8	75.4	13.8	65
EN-QRD-template-8-short text	84.6	3.1	12.3	65
DE-Model-template-short text	93.3	1.3	5.3	75
DE-QRD-template-7.3.1-short text	31.9	59.7	8.3	72
DE-QRD-template-8-short text	89.0	4.1	6.8	73
DE-Model-template-BfArM text	77.4	7.5	15.1	93
DE-QRD-template-7.3.1-BfArM text	31.2	54.8	14.0	93
DE-QRD-template-8-BfArM text	73.4	22.3	4.3	94

EN = English, DE = German, n = number of participants

Interactions between medicines already being taken and those newly prescribed must be taken into consideration to ensure safe use of any medicine. Therefore, participants were asked to locate an example medicine which was listed in the package leaflet for treating heart rhythm disorders which causes interactions with Enal. All short text versions included the answer to this question under the subheading 'Taking other medicines' (model template and QRD template 7.3.1 and 'Other medicines and Enal' (QRD template 8), while the three BfArM package leaflets presented this information in the section 'Take special care'/'Warnings and precautions' section rather than the sections where interactions with other medicines were described. There were no significant differences in the number of correct answers, wrong answers or not found answers given by the participants between the three template versions of each group, although for the short text versions QRD template 7.3.1 provided the most not found answers (table 48).

Table 48: Percent correct, wrong and not found answers for each package leaflet for the question 'Name one medicine that is used to treat heart rhythm disorders which can influence Enal.'

Package leaflet	Name one medicine that is used to treat heart rhythm disorders which can influence Enal. (%)			n
	Correct answers	Wrong answers	Not found answers	
EN-Model-template-short text	92.5	1.5	6.0	67
EN-QRD-template-7.3.1-short text	84.6	0	15.4	65
EN-QRD-template-8-short text	89.2	3.1	7.7	65
DE-Model-template-short text	86.7	5.3	8.0	75
DE-QRD-template-7.3.1-short text	84.7	2.8	12.5	72
DE-QRD-template-8-short text	93.2	1.4	5.5	73
DE-Model-template-BfArM text	28.0	20.4	51.6	93
DE-QRD-template-7.3.1-BfArM text	35.5	23.7	40.9	93
DE-QRD-template-8-BfArM text	30.9	26.6	42.6	94

EN = English, DE = German, n = number of participants

It was also investigated whether participants could find what they should do if they were already taking a medicine to reduce blood sugar levels before taking Enal, namely inform their doctor (table 49). This information was contained in every leaflet version in section 2 under a subheading regarding interactions. All text versions with the model template produced the most correct answers although this was not significant in either country. No significant differences were found in the number of wrong answers or not found answers in England or Germany.

Table 49: Percent correct, wrong and not found answers for each package leaflet for the question 'What should you do if you already take medicines to reduce blood sugar levels and also need Enal?'

Package leaflet	What should you do if you already take medicines to reduce blood sugar levels and also need Enal? (%)			n
	Correct answers	Wrong answers	Not found answers	
EN-Model-template-short text	98.5	0	1.5	67
EN-QRD-template-7.3.1-short text	87.7	6.2	6.2	65
EN-QRD-template-8-short text	98.5	0	1.5	65
DE-Model-template-short text	93.3	1.3	5.3	75
DE-QRD-template-7.3.1-short text	93.1	0	6.9	72
DE-QRD-template-8-short text	91.8	0	8.2	73
DE-Model-template-BfArM text	76.3	6.5	17.2	93
DE-QRD-template-7.3.1-BfArM text	68.8	20.4	10.8	93
DE-QRD-template-8-BfArM text	71.3	19.1	9.6	94

EN = English, DE = German, n = number of participants

The effects of drinking alcohol when taking medicines are often unpredictable or lead to increased adverse reactions. Patients should therefore be able to easily locate this information. Package leaflets with the model leaflet and QRD template 7.3.1 contained information on taking the medicine with alcohol under the headings 'Food and drink' and 'Taking Enal with food and drink' respectively while leaflets with QRD template 8 used the heading 'Enal with food, drink and alcohol'. A common answer which was given when the long BfArM text had been read was that participants simply copied what was written in the leaflet i.e. that alcohol can increase the blood pressure lowering effect of ACE-inhibitors. Although this response is not incorrect in itself, it was considered to be as a wrong answer as participants didn't come to the conclusion relating to the correct action that alcohol should be avoided. This led to the large number of wrong answers for the three BfArM package leaflet versions (table 50). No significant differences were found between the template versions of each group in the number of correct answers. A significant difference was found between the number of not found answers between the QRD template 7.3.1 and QRD template 8 on the case of the long BfArM text ($p = 0.008$, appendix 23). There were no significant differences in the number of wrong answers between any template versions.

Table 50: Percent correct, wrong and not found answers for each package leaflet for the question 'What should you do with regard to drinking alcohol when taking this medicine?'

Package leaflet	What should you do with regard to drinking alcohol when taking this medicine? (%)			n
	Correct answers	Wrong answers	Not found answers	
EN-Model-template-short text	100	0	0	67
EN-QRD-template-7.3.1-short text	100	0	0	65
EN-QRD-template-8-short text	100	0	0	65
DE-Model-template-short text	98.7	1.3	0	75
DE-QRD-template-7.3.1-short text	98.6	0	1.4	72
DE-QRD-template-8-short text	98.6	0	1.4	73
DE-Model-template-BfArM text	54.8	39.8	5.4	93
DE-QRD-template-7.3.1-BfArM text	55.9	34.4	9.7	93
DE-QRD-template-8-BfArM text	59.6	39.4	1.1	94

EN = English, DE = German, n = number of participants

Table 51: Percent correct, wrong and not found answers for each package leaflet for the question 'What is Enal used for treating in children?'

Package leaflet	What is Enal used for treating in children? (%)			n
	Correct answers	Wrong answers	Not found answers	
EN-Model-template-short text	100	0	0	67
EN-QRD-template-7.3.1-short text	100	0	0	65
EN-QRD-template-8-short text	100	0	0	65
DE-Model-template-short text	100	0	0	75
DE-QRD-template-7.3.1-short text	95.8	1.4	2.8	72
DE-QRD-template-8-short text	97.3	0	2.7	73
DE-Model-template-BfArM text	95.7	0	4.3	93
DE-QRD-template-7.3.1-BfArM text	96.8	0	3.2	93
DE-QRD-template-8-BfArM text	91.5	3.2	5.3	94

EN = English, DE = German, n = number of participants

Information regarding what Enal can be used for treating in children was contained in section 3 ‘How to take Enal’ in the short text versions. The longer BfArM text versions had this information in sections 2 (‘Warnings and precautions’) and 3 (‘How to take Enal’). For leaflets with the model template and short text, 100% of subjects located and provided the correct answer in Germany and England, which also applied to the two other leaflets tested in England (table 51). No significant differences were found for the number of correct answers, wrong answers or not found answers between the three template versions in each package leaflet group.

4.7.7 Analysis of comprehensibility and ease of location information in section 3 of the package leaflet

Participants were asked to provide the starting dose of Enal to treat high blood pressure in adults (table 52). For the short text versions the starting dose was provided in ‘number of tablets’ while for the long BfArM text version the milligrams of active ingredient were noted which corresponded to the manner in which the starting dose was described in the particular leaflet versions. There were no significant differences in the number of correct answers found between the three template versions when the number of tablets was noted rather than milligrams. However, there was a significant difference in the number of not found answers in leaflets with the long BfArM text between the model template and QRD template 7.3.1 ($p = 0.022$) and the QRD template 7.3.1 and QRD template 8 ($p < 0.001$, appendix 22). There is no obvious explanation for the large number of not found answers for the BfArM text and QRD template 7.3.1. There were no significant differences found between the number of wrong answers provided with any template version.

Accidentally forgetting to take a dose of medicine is a possible occurrence which causes patients to be uncertain as to how they should act - should they take a double dose to make up for the forgotten dose? Participants provided the greatest number of correct answers for all leaflets tested using the model template but this difference was not significant (table 53). Also, no significant differences were found in the number of wrong or not found answers between the three template versions.

Table 52: Percent correct, wrong and not found answers for each package leaflet for the question 'What is the starting dose of Enal to treat high blood pressure in adults?'

Package leaflet	What is the starting dose of Enal to treat high blood pressure in adults? (%)			n
	Correct answers	Wrong answers	Not found answers	
EN-Model-template-short text	98.5	0	1.5	67
EN-QRD-template-7.3.1-short text	100	0	0	65
EN-QRD-template-8-short text	100	0	0	65
DE-Model-template-short text	98.7	1.3	0	75
DE-QRD-template-7.3.1-short text	97.2	2.8	0	72
DE-QRD-template-8-short text	97.3	2.7	0	73
DE-Model-template-BfArM text	90.3	7.5	2.2	93
DE-QRD-template-7.3.1-BfArM text	80.6	6.5	12.9	93
DE-QRD-template-8-BfArM text	87.2	12.8	0	94

EN = English, DE = German, n = number of participants

Table 53: Percent correct, wrong and not found answers for each package leaflet for the question 'What should you do if you forget to take a dose of this medicine?'

Package leaflet	What should you do if you forget to take a dose of this medicine? (%)			n
	Correct answers	Wrong answers	Not found answers	
EN-Model-template-short text	100	0	0	67
EN-QRD-template-7.3.1-short text	93.8	3.1	3.1	65
EN-QRD-template-8-short text	96.9	3.1	0	65
DE-Model-template-short text	98.7	1.3	0	75
DE-QRD-template-7.3.1-short text	97.2	2.8	0	72
DE-QRD-template-8-short text	94.5	4.1	1.4	73
DE-Model-template-BfArM text	94.6	4.3	1.1	93
DE-QRD-template-7.3.1-BfArM text	87.1	10.8	2.2	93
DE-QRD-template-8-BfArM text	86.2	10.6	3.2	94

EN = English, DE = German, n = number of participants

Taking too much of a medicine can lead to overdose, therefore patients should swiftly be able to locate relevant information on how they should act. This question was answered correctly in all cases in England and for the long text version with QRD template 8 in Germany (table 54). There were no significant differences between template versions in the number of correct and wrong answers given including not located information.

Table 54: Percent correct, wrong and not found answers for each package leaflet for the question 'What should you do if you have taken too much Enal?'

Package leaflet	What should you do if you have taken too much Enal? (%)			n
	Correct answers	Wrong answers	Not found answers	
EN-Model-template-short text	100	0	0	67
EN-QRD-template-7.3.1-short text	100	0	0	65
EN-QRD-template-8-short text	100	0	0	65
DE-Model-template-short text	97.3	2.7	0	75
DE-QRD-template-7.3.1-short text	91.7	5.6	2.8	72
DE-QRD-template-8-short text	95.9	2.7	1.4	73
DE-Model-template-BfArM text	96.8	2.2	1.1	93
DE-QRD-template-7.3.1-BfArM text	94.6	2.2	3.2	93
DE-QRD-template-8-BfArM text	100	0	0	94

EN = English, DE = German, n = number of participants

Before a patient stops taking an antihypertensive medicine, a doctor must be consulted. With QRD template 7.3.1 some participants were of the opinion that the dose should be gradually reduced although it is clearly stated in all versions that a doctor must be consulted. A significant difference was found in the number of correct answers provided between QRD template 7.3.1 and QRD template 8 for the BfArM text versions only ($p = 0.035$, appendix 16) (table 55). No further significant differences occurred for this question between any template versions.

Table 55: Percent correct, wrong and not found answers for each package leaflet for the question 'What should you do if you want to stop taking this medicine?'

Package leaflet	What should you do if you want to stop taking this medicine? (%)			n
	Correct answers	Wrong answers	Not found answers	
EN-Model-template-short text	98.5	0	1.5	67
EN-QRD-template-7.3.1-short text	95.4	0	4.6	65
EN-QRD-template-8-short text	100	0	0	65
DE-Model-template-short text	98.7	0	1.3	75
DE-QRD-template-7.3.1-short text	100	0	0	72
DE-QRD-template-8-short text	97.3	0	2.7	73
DE-Model-template-BfArM text	91.4	3.2	5.4	93
DE-QRD-template-7.3.1-BfArM text	82.8	10.8	6.5	93
DE-QRD-template-8-BfArM text	92.6	6.4	1.1	94

EN = English, DE = German, n = number of participants

Furthermore, participants were asked to provide information relating to duration of use which was stated in all leaflets to be determined by a doctor. For the long BfArM versions tested in Germany, a significant difference in the number of correct answers ($p = 0.002$) and not located answers ($p = 0.007$) was found between the model template and QRD template 7.3.1 only (table 56, appendices 16 and 23). No other significant differences were found between template versions for the number of correct answers, wrong answers or not found answers.

Table 56: Percent correct, wrong and not found answers for each package leaflet for the question 'How long should Enal be used?'

Package leaflet	How long should Enal be used? (%)			n
	Correct answers	Wrong answers	Not found answers	
EN-Model-template-short text	92.5	1.5	6.0	67
EN-QRD-template-7.3.1-short text	92.3	0	7.7	65
EN-QRD-template-8-short text	90.8	1.5	7.7	65
DE-Model-template-short text	90.7	1.3	8.0	75
DE-QRD-template-7.3.1-short text	93.1	1.4	5.6	72
DE-QRD-template-8-short text	91.8	2.7	5.5	73
DE-Model-template-BfArM text	77.4	15.1	7.5	93
DE-QRD-template-7.3.1-BfArM text	57.0	23.7	19.4	93
DE-QRD-template-8-BfArM text	68.1	20.2	11.7	94

EN = English, DE = German, n = number of participants

4.7.8 Analysis of comprehensibility and ease of location of information in section 4 of the package leaflet

The occurrence of side effects is always possible when taking any medication and therefore the participants ease in locating a particular side effect and their frequency in package leaflets was investigated using the side effect example 'hair loss'. Participants provided the most correct answers in England and in the case of the short German package leaflets when using the model template, while QRD template 8 showed the most correct answers for the long BfArM text version (table 57). There were significant differences in the number of correct answers found for the long BfArM text between the model template and QRD template 8 ($p = 0.031$) and QRD template 7.3.1 and 8 ($p = 0.006$, appendix 16). For the long BfArM text there were significant differences in the number of wrong answers between the model template and QRD template 7.3.1 and the QRD template 7.3.1 and QRD template 8 (both $p < 0.001$, appendix 19). Here, the most commonly provided wrong answer was that hair loss was 'rare' rather than 'uncommon'. There were also significant differences between the number of not found answers between the model template and QRD template 7.3.1 ($p = 0.021$) and the model template and QRD template 8 ($p = 0.021$) for the long BfArM text (appendix 22). For the short text versions there were no significant differences in the number of correct answers, wrong answers or not found answers between template versions.

Table 57: Percent correct, wrong and not found answers for each package leaflet for the question 'How frequent is the side effect 'hair loss'?'

Package leaflet	How frequent is the side effect 'hair loss'? (%)			n
	Correct answers	Wrong answers	Not found answers	
EN-Model-template-short text	100	0	0	67
EN-QRD-template-7.3.1-short text	98.5	1.5	0	65
EN-QRD-template-8-short text	93.8	4.6	1.5	65
DE-Model-template-short text	93.4	6.6	0	75
DE-QRD-template-7.3.1-short text	90.3	8.3	1.4	72
DE-QRD-template-8-short text	90.4	4.1	5.5	73
DE-Model-template-BfArM text	65.6	5.4	29.0	93
DE-QRD-template-7.3.1-BfArM text	63.4	20.5	16.1	93
DE-QRD-template-8-BfArM text	79.8	5.3	14.9	94

EN = English, DE = German, n = number of participants

The frequency of side effects can be misunderstood meaning that users believe a side effect occurs much more often than it actually does[183]. The location for describing the frequencies of side effects differed between versions of the leaflet (see package leaflets attached in appendices 4 - 12). For QRD template 7.3.1, a table was used at the start of section 4, while for the model template and QRD template 8, the frequencies were included in subheadings in the side effect list of each frequency group. The side effects in QRD template 8 were also described according to the recommendations in the annotated template with most serious side effects and required actions listed first followed by a list of all other side effects in order of decreasing frequency. The terms used to describe frequencies differed between the different template versions as follows in the case of the 'common' frequency:

- Model template - '**Common,** affects 1 to 10 per 100 people'[60,120,182]
- QRD template 7.3.1 - 'Common - less than 1 in 10, but more than 1 in 100 patients'[36]
- QRD template 8 - '**Common:** may affect up to 1 in 10 people'[48,49]

Participants were asked to write down in numbers the side effect frequency explanation, using the following format: ' <...> of <.....> people', relating to how many people are affected by a side effect if it is 'rare'. The model template and QRD template 8 provided 100 % correct answers in England (table 58). There were no significant differences in the number of correct answers, wrong answers or not found

answers between the three template versions although QRD template 7.3.1 package leaflets showed the lowest number of correct answers.

Table 58: Percent correct, wrong and not found answers for each package leaflet for the question 'How many people are affected by a side effect if it is 'rare'?'

Package leaflet	How many people are affected by a side effect if it is 'rare'? (%)			n
	Correct answers	Wrong answers	Not found answers	
EN-Model-template-short text	100	0	0	67
EN-QRD-template-7.3.1-short text	95.4	1.5	3.1	65
EN-QRD-template-8-short text	100	0	0	65
DE-Model-template-short text	96.0	4.0	0	75
DE-QRD-template-7.3.1-short text	90.3	5.6	4.2	72
DE-QRD-template-8-short text	98.6	1.4	0	73
DE-Model-template-BfArM text	93.5	2.2	4.3	93
DE-QRD-template-7.3.1-BfArM text	90.3	7.5	2.2	93
DE-QRD-template-8-BfArM text	92.6	6.4	1.1	94

EN = English, DE = German, n = number of participants

The SmPC Guideline describes a convention which should be used for frequency groupings e.g. 'rare (≥1/10,000 to <1/1,000)' which is most closely adhered to in QRD template 7.3.1[184]. This definition clearly thereby defines that the frequency of rare side effects is that less than 1 in 1,000 users are affected. Due to the complexity of this manner of description, the method used in the model template was developed and tested in a previous study[52,60]. However, the formulation used in QRD template 8 most frequently led to an overestimation of the frequency of side effects when participants were asked how often a 'rare' side effect occurs (table 59). The method of description used in the model template caused the least overestimation of frequency.

Table 59: Answers to the question: 'How many people are affected by a side effect if it is rare?'

Description of frequency provided by the participants	Subjects (%)					
	QRD-template 7.3.1		QRD-template 8		Model template	
	DE	UK	DE	UK	DE	UK
1 - 10 people from 10,000	1.9	3.2	0	0	90.2	97.0
Less than 1 in 1000 but more than 1 in 10,000	64.3	82.3	0	1.5	0	0
1 in 1000*	23.0	12.9	97.5	98.5	1.8	0
1 in 10*	0	0	0.6	0	1.2	0
1 in 10,000	6.4	1.6	0.6	0	1.8	1.5
1000 to 10,000	1.3	0	0	0	0	0
1 to 10 in 1000*	0	0	0	0	2.5	0
10 from 10,000*	0	0	0	0	2.5	1.5
1 from 100*	2.5	0	1.2	0	0	0
<0.1 % - >0.01 %	0.6	0	0	0	0	0
Number of participants who provided frequencies in numbers	157	62	163	65	163	67

(Grey shading shows the method of frequency description used for each template version. * An asterisk indicates overestimation of the frequency compared to the SmPC definition)

Participants were also asked to identify in which frequency group a side effect belonged if it affected 5 in 100 people. QRD template 8 readers had great problems deriving this information from the leaflet in all three text versions (table 60). There were significant differences in the number of correct answers provided between all leaflet versions ($p \leq 0.031$, appendices 14, 15 and 16). With regard to the number of not found answers in the short English text, significant differences were found between the model template and QRD template 8 ($p = 0.013$) and QRD templates 7.3.1 and 8 ($p = 0.049$, appendix 20). For the German long BfArM text and short text versions, significant differences in the number of not found answers were also found between the model template and QRD template 8, and QRD template 7.3.1 and 8 ($p \leq 0.001$, appendices 21 and 23). The model template in England produced significantly fewer wrong answers than either of the QRD templates ($p \leq 0.002$, appendix 17). In Germany, there was a significant difference in the number of wrong answers between all template versions regardless of whether long or short text had been read; however, with an advantage for the model template ($p \leq 0.013$, appendices 18 and 19). The most common wrong answer given when leaflets with QRD template 7.3.1 and 8 had been

read was that the participants believed that a side effect which affected 5 in 100 people was uncommon rather than common.

Table 60: Percent correct, wrong and not found answers for each package leaflet for the question 'In which of the side effect frequency groups does the following frequency: 'affects 5 in 100 people' belong?'

Package leaflet	In which of the side effect frequency groups does the following frequency: 'affects 5 in 100 people' belong? (average (%))			n
	Correct answers	Wrong answers	Not found answers	
EN-Model-template-short text	85.1	3.0	11.9	67
EN-QRD-template-7.3.1-short text	63.1	21.5	15.4	65
EN-QRD-template-8-short text	36.9	33.8	29.2	65
DE-Model-template-short text	85.3	2.7	12.0	75
DE-QRD-template-7.3.1-short text	70.8	22.2	6.9	72
DE-QRD-template-8-short text	34.2	31.5	34.2	73
DE-Model-template-BfArM text	75.3	7.5	17.2	93
DE-QRD-template-7.3.1-BfArM text	60.2	23.7	16.1	93
DE-QRD-template-8-BfArM text	29.8	30.9	39.4	94

EN = English, DE = German, n = number of participants

Knowing how to act is important if any side effects should occur, that is to contact a healthcare professional. The wording at the end of section 4 regarding how to act when side effects occur differed between each version of the leaflet as shown:

- Model template - 'Always inform your doctor or pharmacist if you notice side effects'.
- QRD template 7.3.1 - 'If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist'[51].
- QRD template 8 - 'If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet'[49].

The wording in QRD templates 7.3.1 and 8 reflects the mandatory statements included in these versions. Patients were asked how to act if they should notice the side effect 'runny nose'. QRD template 8

provided the most correct answers for short and long text versions in both countries (table 61). There was a significant difference between the number of correct answers in the long text version between the model template and QRD template 8 in Germany ($p = 0.009$, appendix 16). In England there were significant differences in the number of correct answers between the model template and QRD template 7.3.1 ($p < 0.001$), QRD template 7.3.1 and 8 ($p < 0.001$) and the model template and QRD template 8 ($p = 0.012$) (appendix 14).

The difference in the number of wrong answers was significant between the model template and QRD template 7.3.1, but also between QRD template 7.3.1 and QRD template 8 ($p < 0.001$, appendix 17) in England. There were also significant differences in the number of not found answers between the model template and QRD template 8 ($p = 0.021$, appendix 20) and the QRD template 7.3.1 and QRD template 8 ($p < 0.001$, appendix 20). In Germany the number of wrong answers found was significant for the short text between QRD template 7.3.1 and QRD template 8 ($p = 0.008$, appendix 18). The number of not found answers was significant in the German long BfArM text version between the model template and both QRD templates ($p \leq 0.005$, appendix 23).

The large number of wrong answers for QRD template 7.3.1 was caused by participants repeating the template wording that a doctor should be consulted only if the side effect gets serious and not that they should consult a doctor in the case of any side effects. This wording could be also the reason for the large number of not found answers in England using QRD template 7.3.1.

Table 61: Percent correct, wrong and not found answers for each package leaflet for the question 'What should you do if you notice the side effect runny nose?'

Package leaflet	What should you do if you notice the side effect runny nose? (%)			n
	Correct answers	Wrong answers	Not found answers	
EN-Model-template-short text	82.1	3.0	14.9	67
EN-QRD-template-7.3.1-short text	26.2	47.7	26.2	65
EN-QRD-template-8-short text	95.4	1.5	3.1	65
DE-Model-template-short text	78.7	6.7	14.7	75
DE-QRD-template-7.3.1-short text	69.4	15.3	15.3	72
DE-QRD-template-8-short text	83.6	1.4	15.1	73
DE-Model-template-BfArM text	50.5	6.5	43.0	93

Package leaflet	What should you do if you notice the side effect runny nose? (%)			n
	Correct answers	Wrong answers	Not found answers	
DE-QRD-template-7.3.1-BfArM text	55.9	20.4	23.7	93
DE-QRD-template-8-BfArM text	69.1	8.5	22.3	94

EN = English, DE = German, n = number of participants

Some side effects are so serious that a doctor should be consulted immediately and the medication should be discontinued. In leaflets with QRD template 8, these most serious side effects were listed at the start of section 4 as recommended. The model template included these side effects in bold type with the advice that a doctor should be contacted immediately, and leaflets with QRD template 7.3.1 had a section 'countermeasures' where symptoms of the very serious side effects and the instruction to contact a doctor were included.

In Germany, participants who had read both short and long leaflets with QRD template 8 provided the most correct answers, while readers of package leaflets with QRD template 7.3.1 gave the most correct answers in England (table 62). However, there were no significant differences found in the number of correct or wrong answers provided for any template versions. For the number of not found answers, a significant difference was found for the long BfArM text versions between the model template and both QRD templates ($p \leq 0.021$, appendix 22).

Table 62: Percent correct, wrong and not found answers for each package leaflet for the question 'Name one side effect which requires that you immediately contact a doctor.'

Package leaflet	Name one side effect which requires that you immediately contact a doctor. (%)			n
	Correct answers	Wrong answers	Not found answers	
EN-Model-template-short text	88.1	9.0	3.0	67
EN-QRD-template-7.3.1-short text	96.9	1.5	1.5	65
EN-QRD-template-8-short text	93.8	4.6	1.5	65
DE-Model-template-short text	80.0	14.7	5.3	75
DE-QRD-template-7.3.1-short text	86.1	9.7	4.2	72
DE-QRD-template-8-short text	93.2	6.8	0	73

Package leaflet	Name one side effect which requires that you immediately contact a doctor. (%)			n
	Correct answers	Wrong answers	Not found answers	
DE-Model-template-BfArM text	78.5	9.7	11.8	93
DE-QRD-template-7.3.1-BfArM text	75.3	22.6	2.2	93
DE-QRD-template-8-BfArM text	84.0	14.9	1.1	94

EN = English, DE = German, n = number of participants

4.7.9 Analysis of comprehensibility and ease of location of information in section 5 of the package leaflet

For some medicines certain storage conditions are required in order to maintain efficacy. Of vital importance is that all medicines are stored out of the reach of children, therefore location of this information contained in section 5 was examined. In England 100 % correct answers were given for leaflets with the model template and QRD template 8 (table 63). In Germany, participants using the QRD template 8 gave the greatest number of correct answers with both long and short text versions. But there were no significant differences found in the number of correct answers, wrong answers or not found answers for any template versions meaning all three template versions were equally good regarding locatability and comprehensibility of storage information.

Table 63: Percent correct, wrong and not found answers for each package leaflet for the question 'How should Enal be stored in relation to children?'

Package leaflet	How should Enal be stored in relation to children? (%)			n
	Correct answers	Wrong answers	Not found answers	
EN-Model-template-short text	100	0	0	67
EN-QRD-template-7.3.1-short text	98.5	0	1.5	65
EN-QRD-template-8-short text	100	0	0	65
DE-Model-template-short text	97.3	1.3	1.3	75
DE-QRD-template-7.3.1-short text	95.8	2.8	1.4	72
DE-QRD-template-8-short text	98.6	0	1.4	73
DE-Model-template-BfArM text	97.8	0	2.2	93
DE-QRD-template-7.3.1-BfArM text	95.7	4.3	0	93
DE-QRD-template-8-BfArM text	98.9	0	1.1	94

EN = English, DE = German, n = number of participants

4.7.10 Analysis of comprehensibility and ease of location of information in section 6 of the package leaflet

The active ingredient 'enalapril maleate' is only listed in section 6 of the model template. For template version 7.3.1 the active ingredient is listed at the top of the leaflet under the product name and then again in section 6. Template 8 contains the name of the active ingredient three times; twice as mentioned for template 7.3.1 and then again in section 1 in the first sentence 'Enal contains enalapril'. The most common incorrect answer was due to a misunderstanding that the pharmaceutical group 'ACE-inhibitor' was the active ingredient, a problem which is mainly due to the wording in the BfArM text version where the first sentence of section 1 reads 'Enal is an ACE-inhibitor'. In England, 100 % correct answers were given for both the model template and QRD template 7.3.1, while in Germany, the most correct answers were given for QRD template 8 for both long and short text versions (table 64). However, there were no significant differences found in the number of correct, wrong or not found answers for any template versions indicating that mentioning the active ingredient once in the package leaflet is sufficient.

Table 64: Percent correct, wrong and not found answers for each package leaflet for the question 'Name the active substance in Enal'.

Package leaflet	Name the active substance in Enal. (%)			n
	Correct answers	Wrong answers	Not found answers	
EN-Model-template-short text	100	0	0	67
EN-QRD-template-7.3.1-short text	100	0	0	65
EN-QRD-template-8-short text	98.5	0	1.5	65
DE-Model-template-short text	92.0	1.3	6.7	75
DE-QRD-template-7.3.1-short text	95.8	1.4	2.8	72
DE-QRD-template-8-short text	98.6	0	1.4	73
DE-Model-template-BfArM text	78.5	14.0	7.5	93
DE-QRD-template-7.3.1-BfArM text	75.3	23.7	1.1	93
DE-QRD-template-8-BfArM text	81.9	12.8	5.3	94

EN = English, DE = German, n = number of participants

A picture of a tablet being broken was included in leaflets with short text versions. In the long BfArM text leaflets with QRD template 8, the user was told that the tablet could be divided in two equal doses which is an optional sentence in this template version. Use of the BfArM version of the enalapril text led to omission of information regarding whether the tablet can be divided in leaflets with QRD template 7.3.1 or model template. In England, 100% correct answers were given for all leaflets. For the short text versions in Germany, 100% correct answers were given when QRD template 7.3.1 or 8 had been used in the leaflet. There were no significant differences found in the number of correct, wrong or not found answers for any short text leaflets between template versions (table 65).

For the long BfArM versions of the leaflet in Germany there was a significant difference in the number of correct answers provided between the model template and QRD template 8 ($p = 0.001$) and the QRD template 7.3.1 and QRD template 8 ($p = 0.024$, appendix 16). The number of not found answers was also significant between the model template and QRD template 7.3.1 ($p = 0.029$) and the model template and QRD template 8 with the BfArM text ($p < 0.001$, appendix 22).

Table 65: Percent correct, wrong and not found answers for each package leaflet for the question 'Can this tablet be divided?'

Package leaflet	Can this tablet be divided? (%)			n
	Correct answers	Wrong answers	Not found answers	
EN-Model-template-short text	100	0	0	67
EN-QRD-template-7.3.1-short text	100	0	0	65
EN-QRD-template-8-short text	100	0	0	65
DE-Model-template-short text	97.3	1.3	1.3	75
DE-QRD-template-7.3.1-short text	100	0	0	72
DE-QRD-template-8-short text	100	0	0	73
DE-Model-template-BfArM text	37.6	23.7	38.7	93
DE-QRD-template-7.3.1-BfArM text	48.4	28.0	23.7	93
DE-QRD-template-8-BfArM text	66.0	20.2	13.8	94

EN = English, DE = German, n = number of participants

4.8 Participants' opinions on the package leaflet printed in the three templates

In section 2 of the questionnaire, the opinion of the participants was asked to 15 aspects relating to the package leaflet. A Likert scale of five categories was used to evaluate the responses and coded in the SPSS data set with the categories ranging from 1 for 'yes', that is total agreement with the statement, to category 5 for 'no', total disagreement (table 2 in 'Materials and methods' - section 3.3.4).

4.8.1 Opinions on the structure of the package leaflet

The participants' opinions on the structure of the package leaflet were mostly positive and very similar for all leaflets regardless of the length of the text or template used. No significant differences were found between templates used for the opinions on whether the information requested in the questionnaire's part 1 was easy to find, or if all the information which was important was at the start of the leaflet.

A significant difference was found in the opinions on whether each subheading clarifies the information contained in the following section between QRD template 7.3.1 and QRD template 8 when the long BfArM text had been used ($p = 0.010$). No further significant differences were found here (table 66).

Table 66: Participants opinions on the structure of the package leaflet

Package leaflet	Statement						n
	The information requested in part 1 was easy to find.		Each subheading clarifies the information contained in the following section.		I found all information which is of importance to me at the beginning of this package leaflet.		
	Calculated median	Opinion	Calculated median	Opinion	Calculated median	Opinion	
EN-Model-template-short text	1.82	mostly yes	1.39	yes	2.45	mostly yes	67
EN-QRD-template-7.3.1-short text	1.75	mostly yes	1.44	yes	2.29	mostly yes	65
EN-QRD-template-8-short text	1.75	mostly yes	1.32	yes	2.18	mostly yes	65
DE-Model-template-short text	1.65	mostly yes	1.23	yes	2.10	mostly yes	75
DE-QRD-template-7.3.1-short text	1.72	mostly yes	1.28	yes	2.10	mostly yes	72
DE-QRD-template-8-short text	1.64	mostly yes	1.27	yes	2.29	mostly yes	73
DE-Model-template-BfArM text	2.25	mostly yes	1.43	yes	2.55	neutral	93
DE-QRD-template-7.3.1-BfArM text	2.51	neutral	1.54	mostly yes	2.63	neutral	93
DE-QRD-template-8-BfArM text	2.27	mostly yes	1.36	yes	2.69	neutral	94

EN = English, DE = German, n = number of participants

4.8.2 Opinions on the comprehensibility of the package leaflet

Participants were of the opinion that the short text package leaflets were easy to understand and a neutral assessment was provided in the case of the longer BfArM text when using the QRD templates 7.3.1 or 8. Significant differences were found in the responses in England between the QRD template 7.3.1 and QRD template 8 ($p = 0.015$) and in Germany for the BfArM text between the model template and QRD template 7.3.1 ($p = 0.045$). No further significant differences were found for opinions on how difficult the package leaflets were to understand (table 67).

Similar opinions as to whether complicated sentences had been used were found for all leaflet versions and participants found that the longer BfArM text contained difficult words. No significant differences between the three template versions of each package leaflet group were found as to whether complicated sentences or difficult words had been used in the package leaflet (table 67).

Table 67: Participants opinions on the comprehensibility of the package leaflet

Package leaflet	Statement						
	The content of this package leaflet was easy to understand.		Complicated sentences were not used in this package leaflet.		This package leaflet does not contain difficult words.		n
	Calculated median	Opinion	Calculated median	Opinion	Calculated median	Opinion	
EN-Model-template-short text	1.76	mostly yes	1.80	mostly yes	1.78	mostly yes	67
EN-QRD-template-7.3.1-short text	1.92	mostly yes	1.76	mostly yes	1.77	mostly yes	65
EN-QRD-template-8-short text	1.64	mostly yes	1.65	mostly yes	1.69	mostly yes	65
DE-Model-template-short text	1.57	mostly yes	1.60	mostly yes	2.41	mostly yes	75
DE-QRD-template-7.3.1-short text	1.70	mostly yes	1.70	mostly yes	2.39	mostly yes	72
DE-QRD-template-8-short text	1.61	mostly yes	1.59	mostly yes	2.33	mostly yes	73
DE-Model-template-BfArM text	2.38	mostly yes	2.68	neutral	4.21	mostly no	93
DE-QRD-template-7.3.1-BfArM text	3.00	neutral	2.90	neutral	4.38	mostly no	93
DE-QRD-template-8-BfArM text	2.55	neutral	3.15	neutral	4.30	mostly no	94

EN = English, DE = German, n = number of participants

4.8.3 Opinions on the information contained in the package leaflets

Participants in general felt well informed from the information contained in the package leaflet and there was only a significant difference found between QRD template 7.3.1 and QRD template 8 in England ($p = 0.045$). No other significant differences were found between template versions (table 68).

In Germany, there was a significant difference in participants' responses as to whether the package leaflet contained too much information between the model template and QRD template 7.3.1 when the BfArM text had been used ($p = 0.031$). No other significant differences were found between template versions with regard to this question or the opinions on whether information on the medicine was missing from the leaflet.

Participants mostly agreed that the package leaflet provided all the instructions needed to use the medicine regardless of the template or text version which had been used. When the BfArM text had been used there was a significant difference in the participants' opinion between the model template and QRD template 7.3.1 ($p = 0.004$) and the QRD template 7.3.1 and QRD template 8 ($p = 0.004$), otherwise no significant differences were found.

Table 68: Participants' opinion on the information contained in the package leaflet

Package leaflet	Statement								
	I feel well informed from the information contained within this package leaflet.		This package leaflet did not contain too much information for me.		No information about the medicine is missing from the package leaflet.		This package leaflet provided all the instructions I needed to use the medicine.		n
	Calculated median	Opinion	Calculated median	Opinion	Calculated median	Opinion	Calculated median	Opinion	
EN-Model-template-short text	1.49	yes	2.07	mostly yes	2.11	mostly yes	1.49	yes	67
EN-QRD-template-7.3.1-short text	1.59	mostly yes	2.32	mostly yes	2.11	mostly yes	1.57	mostly yes	65
EN-QRD-template-8-short text	1.41	yes	2.54	neutral	1.90	mostly yes	1.38	yes	65
DE-Model-template-short text	1.48	yes	2.21	mostly yes	1.67	mostly yes	1.52	mostly yes	75
DE-QRD-template-7.3.1-short text	1.48	yes	2.33	mostly yes	1.51	mostly yes	1.52	mostly yes	72
DE-QRD-template-8-short text	1.39	yes	2.24	mostly yes	1.50	yes	1.52	mostly yes	73
DE-Model-template-BfArM text	1.74	mostly yes	3.13	neutral	1.73	mostly yes	1.66	mostly yes	93
DE-QRD-template-7.3.1-BfArM text	1.99	mostly yes	3.76	mostly no	1.98	mostly yes	2.16	mostly yes	93
DE-QRD-template-8-BfArM text	1.82	mostly yes	3.63	mostly no	1.86	mostly yes	1.76	mostly yes	94

EN = English, DE = German, n = number of participants

4.8.4 Opinions on the readability and motivation to read the package leaflet

Participants who had read a long BfArM version of the package leaflet were less motivated to read the leaflet further than those who had read short versions of the leaflet (table 69). For the short text version in Germany there was a significant difference found between participants' motivation to read the leaflet between the model template and QRD template 7.3.1 ($p = 0.014$) and the model template and QRD template 8 ($p = 0.004$). No other significant differences in motivation were found between templates.

All participants were mostly of the opinion that the text was easy to read and no significant differences were found between leaflet versions.

Table 69: Participants opinion on the readability and motivation to read the package leaflet

Package leaflet	Statement				n
	The first impression of this package leaflet motivated me to read further.		The text is easy to read.		
	Calculated median	Opinion	Calculated median	Opinion	
EN-Model-template-short text	2.93	neutral	1.53	mostly yes	67
EN-QRD-template-7.3.1-short text	2.68	neutral	1.40	yes	65
EN-QRD-template-8-short text	2.49	mostly yes	1.44	yes	65
DE-Model-template-short text	2.29	mostly yes	1.25	yes	75
DE-QRD-template-7.3.1-short text	2.73	neutral	1.31	yes	72
DE-QRD-template-8-short text	2.82	neutral	1.36	yes	73
DE-Model-template-BfArM text	3.73	mostly no	1.94	mostly yes	93
DE-QRD-template-7.3.1-BfArM text	4.00	mostly no	2.20	mostly yes	93
DE-QRD-template-8-BfArM text	4.11	mostly no	2.16	mostly yes	94

EN = English, DE = German, n = number of participants

4.8.5 Opinions on confidence in the package leaflet and the medicine

Whether a patient takes a medicine or not can be affected by concerns which develop after reading the leaflet. Participants' response as to whether the content of the package leaflet raised their concerns about using the medicine were usually neutral, or they had no confidence in taking the medicine (table 70). There were significant differences found in Germany for the short text between the model template and QRD template 7.3.1 ($p = 0.037$) and the BfArM text between the model template and QRD template 8 ($p = 0.023$). Further significant differences were not found.

Regardless of which text had been used or template, participants mostly agreed that taking the medicine outweighed the potential risks (table 70). No significant differences were found here between template versions in any leaflet group.

In Germany, participants were mainly of a neutral opinion in response to the question 'Would you like all package leaflets to be similar to this one?' (table 70). QRD template 8 was evaluated most negatively for the BfArM text version. There were significant differences found regarding the statement 'Would you like all package leaflets to be similar to this one?' for the long BfArM text version between the model template and QRD template 7.3.1 ($p = 0.041$) and the model template and QRD template 8 ($p = 0.008$). In England, no significant differences were found between template versions or in Germany between the short text versions of the package leaflet.

Table 70: Participants' opinions on confidence in the package leaflet and the medicine

Package leaflet	Question						n
	The content of this package leaflet does not raise my concerns about using this medicine.		Does the benefit of taking this medicine outweigh the potential risks?		Would you like all package leaflets to be similar to this one?		
	Calculated median	Opinion	Calculated median	Opinion	Calculated median	Opinion	
EN-Model-template-short text	3.64	mostly no	2.32	mostly yes	2.31	mostly yes	67
EN-QRD-template-7.3.1-short text	3.80	mostly no	2.34	mostly yes	2.30	mostly yes	65
EN-QRD-template-8-short text	3.50	neutral	2.23	mostly yes	2.08	mostly yes	65
DE-Model-template-short text	2.89	neutral	2.34	mostly yes	1.93	mostly yes	75
DE-QRD-template-7.3.1-short text	3.34	neutral	2.63	neutral	2.15	mostly yes	72
DE-QRD-template-8-short text	3.21	neutral	2.67	neutral	2.09	mostly yes	73
DE-Model-template-BfArM text	3.31	neutral	2.56	neutral	2.63	neutral	93
DE-QRD-template-7.3.1-BfArM text	3.74	mostly no	2.62	neutral	3.44	neutral	93
DE-QRD-template-8-BfArM text	3.76	mostly no	2.78	neutral	3.54	mostly no	94

EN = English, DE = German, n = number of participants

4.9 Participants' additional opinions on the package leaflet and suggestions for what should be included or deleted

Layout and design were mentioned in the free-text field at the end of the questionnaire as being a positive aspect for all package leaflets regardless of the template used (table 71). The package leaflet with the model template and short text in Germany were the most liked in terms of layout and design with 53 % of the 75 readers who had read this version noting these as positive aspects. The length of the leaflet was considered best for leaflets with the model template and both the long and short text versions. In England, comprehensibility was often noted as being a positive feature of all package leaflets. One participant noted that they liked the contents list in the leaflet with the model template and BfArM text although there was no contents list present in this version of the package leaflet.

Table 71: What the participants liked most about each leaflet noted in the free-text field at the end of the questionnaire

Package leaflet	Number of participants who commended the aspect of the package leaflet mentioned below									
	No info. missing	Layout and design	Readability of font	Length of leaflet	Compre-hensibility	Order of info.	Side effects described well	Contents list	Other	n
EN-Model-template-short text	3	27	7	10	22	3	1	0 (no index)	1	67
EN-QRD-template-7.3.1-short text	5	29	11	3	24	3	0	0	1	65
EN-QRD-template-8-short text	6	26	7	1	29	4	2	0	1	65
DE-Model-template-short text	5	40	17	11	13	4	1	0 (no index)	5	75
DE-QRD-template-7.3.1-short text	5	28	11	3	15	12	0	1	10	72
DE-QRD-template-8-short text	6	28	14	3	13	9	0	3	10	73
DE-Model-template-BfArM text	14	29	11	9	14	13	0	1 (no index)	6	93
DE-QRD-template-7.3.1-BfArM text	7	23	13	1	10	18	3	1	4	93
DE-QRD-template-8-BfArM text	17	32	7	0	9	17	3	2	2	94

EN = English, DE = German, n = number of participants who had read the leaflet, N.B. Some participants provided more than one opinion and some gave no opinion

The length of the leaflet was the factor that many participants disliked for the long BfArM text versions regardless of the template used with around 50 % of readers noting this as a negative aspect for each template (table 72). The comprehensibility was also perceived as being a negative factor for the long BfArM text versions. Although only the short text version had been used in England, around 30 % of the readers still found the length of the leaflet and around 10 % the list of side effects to be too long regardless of the template used. The list of marketing authorisation holders was mentioned specifically as being disliked by several readers.

Table 72: What the participants disliked about the package leaflet noted in the free-text field at the end of the questionnaire

Package leaflet	Number of participants who criticised aspect of the package leaflet mentioned below											
	The inform-ation provided	**Layout and design**	**Trust in the medicine**	**Read-ability of font**	**Length of leaflet**	**Compre-hensib-ility**	**Order and structure of inform-ation**	**Long list of side effects**	**You should always ask the doctor**	**MAH represent-tatives' list**	**Other**	**n**
EN-Model-template-short text	1	1	-	2	20	10	-	10	-	0 (no list)	10	67
EN-QRD-template-7.3.1-short text	0	0	-	0	25	2	-	9	-	1	15	65
EN-QRD-template-8-short text	4	3	-	2	20	2	-	7	-	4	11	65
DE-Model-template-short text	0	2	0	0	4	2	1	8	2	0 (no list)	10	75
DE-QRD-template-7.3.1-short text	1	0	1	3	5	1	0	5	0	0	11	72
DE-QRD-template-8-short text	0	1	0	1	7	1	0	2	2	7	9	73
DE-Model-template-BfArM text	2	1	0	2	43	14	0	2	0	0 (no list)	7	93
DE-QRD-template-7.3.1-BfArM text	3	9	0	2	45	6	0	1	0	2	4	93
DE-QRD-template-8-BfArM text	1	7	0	4	50	9	0	0	0	2	5	94

EN = English, DE = German, n = number of participants who had read the leaflet, N.B. Some participants provided more than one opinion and some gave no opinion

When participants were asked what they thought should be deleted in the package leaflet, the most frequently crossed out information was the MAH representatives' list when present (11.1 to 25.5 % of the participants, table 73). Interestingly, approximately double the amount of readers deleted the list when QRD template 8 had been used rather than QRD template 7.3.1 regardless of whether the long or short text version had been read. The picture of the tablet being divided, which was included in the short text versions, was also deleted by around 5 % of the readers in England.

Table 73: What the participants thought should be deleted in each package leaflet noted in the free-text field at the end of the questionnaire

Content deleted	Package leaflet								
	EN-Model-template-short text	**EN-QRD-template-7.3.1-short text**	**EN-QRD-template-8-short text**	**DE-Model-template-short text**	**DE-QRD-template-7.3.1-short text**	**DE-QRD-template-8-short text**	**DE-Model-template-BfArM text**	**DE-QRD-template-7.3.1-BfArM text**	**DE-QRD-template-8-BfArM text**
Information box	0	0	0	0	1	0	0	0	0
Contents list	0	3	2	0	1	2	0	2	0
Picture of tablet dividing	4	3	5	0	0	1	0	0	0
Section 1	1	0	0	1	0	0	0	0	0
Section 2: Contra-indications	2	0	1	1	0	0	0	0	1
Section 2: Warnings and precautions	3	3	4	1	1	0	0	1	4
Section 2: Interactions	3	2	3	1	0	0	2	5	5
Section2: Food and drink	0	1	0	1	0	0	1	0	0
Sections 2: Ability to drive	0	0	0	1	0	0	0	0	0

Content deleted	Package leaflet								
	EN-Model-template-short text	**EN-QRD-template-7.3.1-short text**	**EN-QRD-template-8-short text**	**DE-Model-template-short text**	**DE-QRD-template-7.3.1-short text**	**DE-QRD-template-8-short text**	**DE-Model-template-BfArM text**	**DE-QRD-template-7.3.1-BfArM text**	**DE-QRD-template-8-BfArM text**
Section 2: Pregnancy and breast-feeding	0	0	2	0	0	0	0	0	3
Section 3: Dosage	3	2	4	1	0	0	2	0	4
Section 3: Method of administration	0	1	2	1	0	0	1	0	1
Section 3: Duration of administration	0	0	0	0	0	0	1	0	2
Section 3: Overdose	0	0	3	0	0	0	1	0	2
Section 3: Stopping taking Enal	0	0	0	0	0	0	1	0	0

Content deleted	Package leaflet								
	EN-Model-template-short text	**EN-QRD-template-7.3.1-short text**	**EN-QRD-template-8-short text**	**DE-Model-template-short text**	**DE-QRD-template-7.3.1-short text**	**DE-QRD-template-8-short text**	**DE-Model-template-BfArM text**	**DE-QRD-template-7.3.1-BfArM text**	**DE-QRD-template-8-BfArM text**
Section 4: Table used for description of side effects frequency	0 (no table)	6	0 (no table)	0 (no table)	1	0 (no table)	0 (no table)	1	0 (no table)
Section 4: All side effects	2	0	0	1	0	0	0	0	0
Section 4: All side effects except very frequent	0	2	4	1	0	0	2	1	2
Section 4: rare side effects	0	0	0	0	0	0	2	2	1
Section 4: Very rare side effects	1	0	0	2	0	0	0	3	1
Composition of the tablet	1	0	1	0	0	0	2	0	2

Content deleted	Package leaflet								
	EN-Model-template-short text	**EN-QRD-template-7.3.1-short text**	**EN-QRD-template-8-short text**	**DE-Model-template-short text**	**DE-QRD-template-7.3.1-short text**	**DE-QRD-template-8-short text**	**DE-Model-template-BfArM text**	**DE-QRD-template-7.3.1-BfArM text**	**DE-QRD-template-8-BfArM text**
MAH representatives' list	0 (no list)	11	19	0 (no list)	8	18	0 (no list)	12	24
Other sources of information	0	0	0	0	0	2	0	1	2
How Enal looks and contents of the pack	0	2	3	0	2	2	0	2	3
Storage information	0	0	0	0	0	1	1	0	3
Date of last revision of package leaflet	0	1	0	0	0	1	1	2	2
Participants (n)	67	65	65	75	72	73	93	93	94

EN = English, DE = German, n = number of participants who had read the leaflet

Most participants did not want any additional information included in the package leaflet (table 74). In England however 26 % of the readers of the leaflet with QRD template 7.3.1 requested an explanation of what ‘special care’ means.

Table 74: What the participants thought should be included in the package leaflet noted in the free-text field at the end of the questionnaire

Package leaflet	Number of participants who thought the information mentioned below should be included in the package leaflet										
	Benefits of medicine	**Price**	**Tablet appear-ance**	**'Use by' date**	**Rx or OTC**	**Website/ NHS direct no.**	**What does 'special care' mean**	**Better dosage instruc-tions**	**Counter measures should stand out more**	**Other**	**n**
EN-Model-template-short text	2	0	0	0	2	1	0	4	1	8	67
EN-QRD-template-7.3.1-short text	0	0	1	0	0	1	17	3	4	4	65
EN-QRD-template-8-short text	3	0	0	0	0	2	0	2	0	10	65
DE-Model-template-short text	3	0	2	0	6	0	0	0	0	8	75
DE-QRD-template-7.3.1-short text	2	0	2	1	0	0	0	0	0	6	72
DE-QRD-template-8-short text	3	0	1	0	0	0	0	0	0	4	73
DE-Model-template-BfArM text	2	1	1	0	1	0	0	0	0	9	93
DE-QRD-template-7.3.1-BfArM text	2	0	4	0	0	0	0	0	0	9	93
DE-QRD-template-8-BfArM text	1	0	4	0	0	0	0	0	0	5	94

EN = English, DE = German, n = number of participants who had read the leaflet

4.10 Dependence of the readability test results on demographic factors

Factors such as age, education level and number of medicines taken a day were investigated relating to their influence on the ability to locate and understand information in the package leaflet and the length of time needed to complete the 26 questions relating to the content of the package leaflet. Participants under 20 years of age answered the 26 content questions most rapidly in Germany but also gave the greatest number of not found answers (table 75). People aged 60 and over needed the longest time to answer the same amount of content questions in Germany. In England, participants aged over 60 answered the content questions most rapidly.

There was a significant difference ($p < 0.001$) found in the time needed to answer the questions relating to package leaflets content when using the long BfArM text between participants in the age groups ≤ 19 and 20 - ≤ 39, ≤ 19 and 40 - ≤ 59, and 40 - ≤ 59 and ≥ 60 (appendix 24).

There were no significant differences found between the age groups in England regarding the length of time needed to answer the content questions. Participants in the 20 - ≤ 39 years age group gave the most correct answers in Germany with the short text version and those aged ≥ 60 with the long BfArM text version.

The age group 40 - ≤ 59 in England provided the most correct answers. There were no significant differences in the number of correct answers, wrong answers or not found answers between the age groups for any leaflet group in England.

The majority of participants took no medicine at the time of the readability test (table 74). There were no significant differences depending of the number of medicines taken per day relating to the number of correct, wrong or not found answers for any groups of leaflets. There was however a significant difference in the length of time needed to answer the questions on content and the number of medicines taken per day for the long BfArM text version ($p \leq 0.016$, appendix 25) in Germany.

Table 75: Number of correct, wrong and not found answers and time needed to provide information for 26 questions relating to content itemised according to age group and package leaflet group summarised for the three readability test rounds

Package leaflet group	Age group (years)	Calculated Median				
		n	Correct answers (%)	Wrong answers (%)	Not found answers (%)	Time to answer 26 content questions (minutes)
EN-short text	20 - ≤ 39	23	89.5	5.0	4.3	15.6
	40 - ≤ 59	12	90.2	5.8	2.1	15.3
	≥ 60	34	89.8	4.8	3.4	13.4
DE-short text	≤ 19	5	88.9	3.8	6.4	19.3
	20 - ≤ 39	21	91.5	5.4	2.7	20.3
	40 - ≤ 59	45	91.0	5.2	2.9	20.6
	≥ 60	5	90.1	5.8	4.3	32.0
DE-BfArM text	≤ 19	35	67.5	14.5	16.3	17.3
	20 - ≤ 39	13	67.9	14.3	16.0	30.0
	40 - ≤ 59	41	75.1	12.1	11.8	32.4
	≥ 60	7	77.7	14.9	3.6	52.5

EN = English, DE = German, n = number of participants

Participants who had an education level up to 8th class in Germany provided the lowest number of correct answers (table 75). However, there was no great variability within the other levels of education and no significant differences were found in the number of correct answers or time needed to answer content questions according to education level.

Table 76: Number of correct, wrong and not found answers and time needed to answer 26 questions relating to the content of the package leaflet itemised according to the number of medicines used per day, summarised for the three readability test rounds

Package leaflet group	Number of medicines taken per day	n	Average age (years)	Calculated Median			
				Correct answers (%)	Wrong answers (%)	Not found answers (%)	Time to answer 26 content questions (minutes)
EN-short text	0	27	48	90.2	4.7	3.2	15.7
	1	22	49	90.6	5.2	3.3	19.0
	2	12	57	88.5	5.3	3.3	20.0
	≥ 3	8	61	87.5	5.1	4.4	21.6
DE-short text	0	50	40	90.0	5.4	3.4	20.6
	1	17	39	92.9	4.0	2.6	19.7
	2	4	42	91.5	3.8	4.9	22.5
	≥ 3	5	69	88.8	6.9	4.8	30.0
DE-BfArM text	0	57	31	79.2	10.8	9.8	24.4
	1	24	38	77.2	11.0	9.3	26.3
	2	8	48	84.6	11.2	2.9	37.5
	≥ 3	7	54	78.6	14.8	6.1	40.0

EN = English, DE = German, n = number of participants

Table 77: Number of correct, wrong and not found answers and length of time needed to answer 26 questions on content of the package leaflet according to education level

Package leaflet group	Level of education	n	Calculated Median			
			Correct answers (%)	Wrong answers (%)	Not found answers (%)	Time to answer 26 content questions (minutes)
EN-short text	10th class	5	92.3	5.5	2.5	19.6
	A-levels	7	88.5	4.6	3.3	16.5
	Polytechnic college	5	91.2	4.5	2.6	21.3
	University	46	89.7	5.1	3.3	19.2
	Other	6	88.5	5.6	5.4	20.0
DE-short text	8th class	7	88.0	6.6	5.0	28.9
	10th class	27	90.7	5.5	3.3	19.9
	A-levels	9	94.1	2.2	2.3	22.0
	Polytechnic college	4	91.7	5.2	2.7	18.3
	University	11	91.5	4.7	3.1	19.7
	Other	18	87.7	6.1	4.3	25.7
DE-BfArM text	8th class	42	69.2	15.7	12.8	20.2
	10th class	12	79.0	10.2	10.6	21.0
	A-levels	10	86.5	7.4	5.0	31.9
	Polytechnic college	8	85.0	9.8	5.1	35.0
	University	18	84.2	7.7	7.7	31.4
	Other	6	81.5	13.2	3.6	32.5

EN = English, DE = German, n = number of participants

5. Discussion

5.1 Qualifying the research context

Although the QRD template has been used since 1996, studies regarding its readability are scarce, a situation which is contrary to the fact that testing of package leaflets themselves is mandatory before they are accepted by the authorities, and the fact that the QRD template must be used for each package leaflet distributed within the European Union and connected countries. The demanded readability testing by the European Commission of package leaflets has also been shown to be beneficial and improve package leaflets' readability[185]. Due to publication of QRD template version 8 (for centralised approved medicines) and version 2 (for other medicines) in 2011, headings and mandatory texts underwent many changes based on information gained from user testing and feedback from various other sources. The concerned user testing results are a collection of problems identified from QRD template version 7.3.1, although the methods and resulting data used to create these amendments remain unpublished[49]. The effects of the increased text volume has not been addressed by the authors of the QRD template even though a study of a German representative sample of package leaflets in the year 2005 found that an average of 17.7 % of the volume of text was caused by the QRD template[54]. The study by Fuchs et al. published in 2010 also demonstrated that over a 5 year period, from 2000 to 2004, that the QRD text in the examined 271 package leaflets increased in volume by 25.1 %[54]. QRD template wording has been demonstrated in some cases to cause misunderstanding, which was found during a readability test involving the QRD template 7 in 2006 which identified comprehensibility problems with some of the headings[186]. A further readability test study published in 2012 with 192 participants showed that 14.1 % of incorrect answers from a group who had read package leaflets with the QRD template were caused by comprehensibility problems with the template wording[52]. In view of the lack of published studies regarding readability of the QRD template, one focus of this project was to test the QRD template 8 which had just been published at the start of this study, and is very similar to the current version 9, in comparison to the predecessor template version, and a model template to identify whether readability and comprehensibility had improved.

Implementation of the QRD template within the European Union, Iceland, Norway and Lichtenstein has served the purpose of creating uniformity in the structure and content of package leaflets which is beneficial for patients as the information which they receive with each medicine is therefore organised in the same way. This is in contrast to some other countries such as the United States where three different types of patient information exist, each with a differing layout and content[187]. Use of a template is not simply a European Union phenomenon; non-EU countries such as Australia, New Zealand, Switzerland and the United States also use documents similar to the QRD template for both the package leaflet and specialist information. A comparative evaluation for consumer medication information was carried out for the United States, Europe (represented by package leaflets from the United Kingdom) and Australia[188].

This study by Raynor et al. published in 2007 involved reviewers evaluating the chosen leaflets and giving each a score according to whether selected criteria had been adhered to, for example, whether certain clinical content is present and whether the form it is written in is legible. Wide variation was found in the quality of the leaflets in terms of content and readability, although it must be taken into consideration that this rating was largely due to personal opinions of the reviewers involved. The Australian leaflets studied by Raynor et al. were generally superior followed by those from the United Kingdom (representing European Union leaflets) and the United States which was suggested to reflect the regulatory context[188]. The lack of clear headings and bullets to enhance readability were mentioned as negative aspects of the United States leaflets. Certain aspects of package leaflets from the United Kingdom, the United States and Australia were evaluated positively, for example, the use of phonetic spelling of the name of the medicine in the United States[188]. Phonetic spelling is also suggested in the core CMI from Australia, but is not a component of the QRD template. The comparative study published by Raynor et al. proposed that leaflets from Australia and the United Kingdom achieved higher scores than those from the United States as they included most or all of the relevant information available to health professionals[188]. There is relatively little research and no existing published studies on the content or design of templates used for the package leaflet, therefore investigation into legislation and guidelines influencing the content of templates from other countries was considered a further important aspect of the study described in this dissertation.

5.2 Methodology

5.2.1 Analysis of QRD template development up to the present day

Since initial publication of the QRD template in 1996, wide ranging changes in structure, headings, subheadings and standard text have taken place. No published study was found regarding template development and therefore part of this work was to analyse versions of the template from the initial publication to the present day. As only the newest version of the QRD template is available on the EMA website, it was necessary to request older versions of the QRD template directly from the EMA. After all versions of the QRD template from the first edition to version 7.3.1 had been kindly provided, the QRD template for centralised procedures for OTC products was used for further analysis, rather than that for MRP/DCP procedures, as a consecutive sequence of older versions of this document were available up to the present day. Only minor differences exist between the template for OTC medicines compared to that for prescription only medicines, for example, in the phrases provided in the information box at the start of the template. The template for MRP/DCP procedures differs to that for centralised procedures at the end of section 6 where instead of a list of representatives of the marketing authorisation holders, the name of the medicine is provided and the country where it is on sale under the given name. The results thereby found in this study concerning the template for OTC medicines authorised via a centralised procedure can

be extrapolated for the most part to the template for prescription only medicines and that for MRP/DCP authorisation procedures.

An important component of QRD template analysis was to determine the minimum and maximum number of words contained in each template version to illustrate how the text volume of the template has developed over time. The number of words present in the QRD template text framework has previously been shown to be increasing in volume[54,189], a fact which could lead to longer package leaflets which has been demonstrated to have a negative effect on locatability of information, reduces motivation to read the package leaflet and increases the time needed to find specific facts[55]. Due to the bracketing convention in the QRD template, sections of the template can be omitted in the package leaflet which are not relevant to the described medication. Therefore this bracketing convention was applied to investigate the minimum number of words which must be used from the template. The choice of parameters which were investigated in each version of the QRD template were selected to assess whether suggestions from the Readability Guideline were put into practice by the QRD group. Long sentences of over 20 words should not be used according to the Readability Guideline from 1998[36], and abbreviations should be avoided[38], therefore these aspects were considered important to analyse. As repeating information causes an increase in text volume, repeated sentences present in each version of the template were counted. A text comparison of the main headings, subheadings and standard sentences in each version of the QRD template was carried out to illustrate how these phrases had developed over time.

5.2.2 The use of templates for the package leaflet in EU and non-EU countries

To meet the aim of comparing the structure and content of information contained in other templates in comparison to the European Union's QRD template, countries were chosen as defined by the criteria described in section 3.2. Although a comparison of templates for the package leaflet was the focus of the study, the investigation into the history of development of legal directives and guidelines influencing the content of the package leaflet in the chosen countries was considered a valuable starting point in order to understand the content of the investigated templates.

A good working knowledge of both the English and German language was an advantage when analysing the templates from the chosen countries. Conversely, a limitation of this study is therefore that templates most probably exist in languages other than the two involved which were not included in the investigation. Other existing templates could be in a different form and potentially better than those investigated. The collection of countries chosen was also not exhaustive of those where English and German is the main language spoken, however, the choice included nations from widely separated points on the globe who published a template via the internet. The necessary directives, guidelines and templates from the selected

countries were also easily accessible on the internet, and it was possible to contact representatives at the relevant authorities and be provided with information.

5.2.3 Evaluation of QRD template implementation in package leaflets of centralised approved medicines

During a time period of two years, all package leaflets for medicines authorised by a centralised approval procedure and accessible on the EMA website were analysed. A similar download and analysis of QRD template use in package leaflets of medicines for centralised approved medicines is not known. The download process of these documents took place three times with a year time gap between each download. A time gap of one year was considered acceptable between downloads to see how rapidly implementation of QRD template 8 and subsequently 9 took place. This study highlighted the enormous effort the pharmaceutical companies and authorities expend in order to ensure up-to-date documents. Over 70 % of the examined package leaflets were updated between each download, although the updates did not always affect QRD template use but rather other aspects of the content. This method was chosen as these documents were publically available and enabled a large number of package leaflets for a wide variety of medicines to be investigated. Although 616 package leaflets were available at the time of the first download, it was not possible to analyse all of them due to technical problems. However, only 8.3 % of the package leaflets could not be analysed, and calculation of the 95 % confidence interval showed that the remaining sample size of 565 package leaflets is representative of the actual situation of package leaflets of centralised approved medicines. However, as only package leaflets for centralised procedures were analysed, differences to the template implementation in package leaflets authorised via purely national procedures can naturally not be excluded due to the fact that each member state has its own specific requirements for national legislation. For example, the Danish authorities request additional information beyond the scope of the QRD template in section 2, 3 and 4 of the package leaflet[179]. In section 2 of the Danish package leaflet the following statement must be present; 'Please notice that your doctor may have prescribed the medicinal product for a different therapeutic indication and/or at a different dosage than stated in the package leaflet. Always follow the doctor's prescription and the instructions on the dosage label'[179]. However, as the QRD template should also be used for national procedures, existing national requirements are placed more in the background. Differences in QRD template use for products authorised via a MR/DC procedure must also be considered, however, are minimal. The QRD template for MR/DC procedures version 3 only differs to that for centralised approved procedures in the less important information in section 6 of the package leaflet, where it includes a section for the names of the medicinal product and member states of the EEA where it is authorised, and does not include the optional list of 30 MAHs representatives. Therefore, the only differences which are to be expected in the implementation of the QRD template for centrally authorised medicinal products compared to those authorised via a MR/DC

procedure affect section 6 and not other elements of the template. One point which is however also no known is how quickly the package leaflets are altered or updated for MR/DC or national procedures compared to those for centralised approved procedures.

5.2.4 Study design of the readability test involving QRD template version 8, its predecessor and a model template version

To comply with Articles 59 (3) and 61 (1) of Council Directive 2001/83/EC as amended by Directive 2004/27/EC, Marketing Authorisation Holders must provide evidence that the package leaflet '*reflects the results of consultations with target patient groups to ensure that it is legible, clear and easy to use*' and these results should be presented to the competent authority[39,24]. This ruling is intended to ensure that patients can locate and comprehend key messages in the patient information for a safe and effective use of medicines. One method of complying with this legal requirement is to carry out a 'user testing', the current gold standard in the EU, of the package leaflet whereby readability of an example is tested with a group of subjects[38,190]. The most frequently used method by MAHs to abide by Article 59 (3) is the 'Australian' method of user testing where verbal face-to-face interviews with participants are carried out in a minimum of two rounds[61]. An alternative to this approach is the 'self-completion' method which takes the form of the written readability test. The written readability test method was chosen in this study to investigate the readability of the QRD templates 7.3.1 and 8, and a model template. This self-completion way of testing is a strength of the study and offers advantages over the 'Australian' method as a more real life situation is simulated whereby participants receive a package leaflet and questionnaire which they fill in independently. This method has been validated in a previous study by Fuchs et al. published in 2007 and complies with the guidelines in the European Union[53,61]. When this method is used, less external influence, such as mimics and gestures, is provided by the interviewer themselves compared to when the interviewer poses the question and fills in the questionnaire, which is essential to compare different leaflet texts[61]. Participants with hearing difficulties could also have problems understanding the interviewer, or conversely the interviewer may not understand the answer provided and write down an alternative response. The written readability test also provides the advantage that it was possible to provide the same conditions in each round of the readability test and country whereby participants received their instructions via the questionnaire and not from an outside person. A slight deviation to the method developed by Fuchs et al.[53] was used in the readability test in this study as the majority of participants were allowed to take the package leaflet and questionnaire home to complete, rather than filling it in under a controlled environment. However, the school classes involved in this study read the material and filled in the questionnaire under observation by a teacher in the classroom. Theoretically participants who filled in the questionnaire at home could have gained help from a further person or deliberately written down the wrong answers, although this behaviour is not to be expected from volunteers. Another point mentioned

by the CMDh is that in comparison to the Australian method, in the written readability test 'participants do have to be capable independently of reading and answering the questionnaire, using only the written instructions provided'[61]. However, it is this fact which ensures identical study conditions in each test round of this template study. It was also additionally explained to each participant personally how to carry out the readability test using the provided materials.

As participants in the user test should be representative of everyone who might take the medicine, people with lower literacy and writing skills must not be excluded. During recruiting in this study, all levels of education where therefore included and the resulting group of participants provided people with a wide range of educational background, age and social status. A limitation however of this study could be that all participants, except for one in England, were native speakers of the language in which the readability test was carried out, meaning that understanding of the materials provided for the readability test by non-native speakers, who may not possess such advanced language skills, could not be investigated. Theoretically, restricted understanding of either German or English could therefore have affected the results of this study. All participants were also volunteers which may have also caused a bias in the results due to those involved being interested and willing to read the information and answer the questionnaire. It is not known how people with no interest in taking part in the study would have performed, although there is no reason to believe the answers provided would differ.

The study design of the readability test described in this work followed a similar structure to that recommended by the CMDh[61] whereby key messages were identified to test the template text, a questionnaire was prepared based on these key messages and on overall perception of the document, followed by completion of the questionnaires by test participants. To test the leaflet using an interview technique, the Readability Guidelines and the CMDh recommend two test rounds with a minimum of 10 participants in each[36,38,61]. The recommended minimum number of 20 participants was exceeded in this study to a three to four times higher number of people who tested each package leaflet in order to obtain robust data. A cross-over study design was chosen whereby each participant tested each template as this allows better comparison of the three templates investigated. A minimum six month time period before each participant tested a new template version of the leaflet was chosen according to the recommendation of the MHRA, whereby 6 months is considered sufficient to avoid participants getting used to knowing where to find information[191]. Leaflets prepared with the three templates had an identical font size and type, paper and print quality. Care was taken that the content of the text provided and layout of information of both the package leaflets and questionnaire used in both countries was identical to ensure best comparison of the tested templates.

5.2.5 Development of package leaflets and questionnaires for the written readability test

Package leaflets were created for the active ingredient enalapril using QRD template 7.3.1, QRD template 8 and a model template which had been tested in previous studies[52,53]. The active ingredient enalapril was chosen as this is a widely used medicine for which a sample text was freely available from the German authorities BfArM at the start of this study[59]. It thereby provided an authentic text which was currently used at the time for enalapril containing products on the German market independent of the marketing authorisation holder or manufacturer. In addition, the text for enalapril has been used in a previous study[55] and although enalapril is not authorised via a centralised procedure, the type of marketing authorisation for this active ingredient was irrelevant to this study as the template text was being tested and not information relating to the product itself.

For the printed material used in this study, a larger type face was used for headings of the main sections and a smaller font size for the running text. In leaflets printed with QRD template 7.3.1, capitals were used for the section headings as this was the chosen format in this template version. Bold type was used in leaflets with the model template to emphasise serious side effects and for all section headings in every leaflet which is mentioned in the Readability Guideline[38].

The purpose of the readability test in this study was to analyse whether the headings and standard statements used in two versions of the QRD template or an alternative model template influence patient understanding in terms of locatability and comprehensibility of information. The questions chosen where therefore specifically designed to test the text from the template rather than any medicine specific information. The order in which the questions were presented was randomised as recommended by the Readability Guideline[36]; questions which referred to information in adjacent sections/paragraphs were not asked in sequence. The study described in this work involved 26 questions relating to content contained in each package leaflet, 12 -15 questions is considered sufficient to test a leaflet[38,178,192]. More than the usual number of questions was included in order to test double the amount of template text than could otherwise be carried out. In a previous study, 25 questions relating to content of a package leaflet were used, and the time expenditure ranged from 5 to 75 minutes (calculated median 20 minutes)[52]. This indicated that using a questionnaire with 26 questions would not overtax participants and that the required time was feasible.

5.3 Comparison of the European Union QRD template to templates used in non-EU countries

The concept of developing a template for the package leaflet in the investigated countries/areas was first seen in Germany in 1993 followed by the publication of the European QRD template in 1996. Core CMIs were introduced in New Zealand in 1998 and in Australia in 2001. Although the templates have arisen from different national legal situations, the order and content of information is surprisingly similar (table

19). This sequence structure in the QRD template, which arose as a result of implementation of Directive 2004/27/EC[24], has been shown in two previous studies to meet both the needs of specialists and patients significantly more than previous valid versions[12].

In a similar manner to the annotated versions of the QRD template, the core CMI in Australia provides precise detail on what to include in each section, while that from New Zealand is very sparse which could lead to greatly differing information being provided by MAHs in each section. An advantage of the examined templates from Switzerland, Australia, New Zealand and the current QRD template from the European Union is that they all provide clear headings placed on a separate line to the main text and avoided the use of italics and capital letters; both which are advised against in the Readability Guideline from 2009[38]. As seen during the analysis of the QRD template development, it is only the most recent versions of the template which avoid use of both italics and capital letters. However, in the readability test described in this study, the use of capital letters in package leaflets with QRD template 7.3.1 was never criticised by the participants.

A study of written medicine information from English speaking countries found that 100 % of Australian leaflets used in the practice, as well as the majority of leaflets from the United Kingdom, separated headings from main text[193]. Emphasis of section titles in capitalised text has been suggested as being difficult to read[193]. A study involving 224 readers, who analysed various headline styles, concluded that those in capital letters were significantly less legible than those in lower case[194]. Use of capital letters also takes up a least one-third more space than lower case and reduces speed of reading[195]. While QRD template versions up to 7.3.1 used bold text in capitals for the main section headings, this was changed from QRD template 8 to lower case letters which can be welcomed as an improvement as bold, lower case letters have been found to be good for emphasis[196,197].

Legislation, templates and guidelines determine the creation of the package leaflet in the European Union and Australia. In the European Union the QRD template should be used in conjunction with the Readability Guideline[38] while the writer of the CMI in Australia is told to refer to the Usability Guidelines[146]. Both these guidelines are intended to improve the readability of patient information. In the United States of America no reference to such documents is present and a study of MedGuides from 2006 to 2011 showed that during this 5 year period that little improvement had been made in readability[198]. Therefore, simply the use of a template to determine structure and content of the patient information appears not enough to increase readability, but that supplementary guidelines regarding layout, design and linguistic style could be helpful. The Plain Writing Act was introduced in the United States in 2010 and a further agency is developing a set of standards for designing materials such as MedGuides which are

hoped to improve readability[198]. A further study published by Luk et al. in 2010 which indicated that use of templates in combination with usability guidelines is beneficial was carried out whereby 157 samples of written medicine information were evaluated by three researchers[193]. The readability of the leaflets was assessed using the Flesch-Kincaid Grade Level which is a mathematical formula designed to calculate the number of years of education generally required to understand a text. This method of assessing readability greatly differs from the readability tests used in the European Union and Australia whereby real people test the package leaflets with regard to locatability and comprehension of contents. The latter offers the advantage that usability is tested in the practice and not calculated using a formula. The results of the readability test in this study also showed that the number of years of education did not affect how participants understood the tested package leaflets which indicates that maybe calculating the number of years of education generally required to understand a text is not the deciding point as to whether the document is comprehensible to certain users or not. The PAINT1 study with 1105 participants confirmed this finding[53].

With regard to the ease of readability, Luk et al. found that written medicine information from New Zealand and Australia was superior to information from the other English speaking countries Canada, Ireland, United States and the United Kingdom, although all used a conversational tone and active voice[193]. This was attributed by the authors to the fact that the information in Australia and New Zealand uses a standardised format (dictated by the templates) and compliance with usability guidelines[193]. Leaflets from the Unites States fared worse than the European leaflets examined which was again ascribed to the lack of standardised guidelines.

It was also of interest to see how different information is included in the package leaflet for the patient in the examined countries. Statements regarding whether the product is addictive are present in the patient information from the United States, Australia and New Zealand, self-help methods to improve the medical condition are found in Australia, New Zealand and Switzerland. Describing the benefits of the medication to improve patient compliance was seen in all examined templates except that from Switzerland. Describing the benefits of a certain medicine has been shown to be positive[199] and therefore inclusion of such information in a template might be advantageous.

In Switzerland, the manufacturer of the product does not have to be mentioned in the package leaflet, only the name and address of the MAH who bring the product onto the market. One study in Germany involving 855 participants revealed that the name of the MAH and manufacturer are considered the least important information in the package leaflet[23]. In this study, all leaflets contained the name of the marketing authorisation holder and manufacturer. However, these components were never mentioned

when participants were asked what they thought should be deleted in the package leaflet. Nonetheless, as the name of the MAH is also a component of the outer packaging, its omission from the QRD template for the package leaflet could be considered. Alternatively, the number of provided addresses could be reduced to one, such as only the MAH thereby omitting the manufacturer.

5.4 Comparison of comprehensibility, location of information and satisfaction with each package leaflet tested in the readability test

The increasing volume of text in the QRD template has contributed to the fact that package leaflets are increasing in length, a fact which is not welcomed by users[1]. A more compact leaflet in the future has also been favoured by specialists[12]. The study described in this work has shown that it is possible to reduce the text volume of a package leaflet by use of a model template and consolidating the text information under a series of bullet points. Using bullet points rather than continuous text to organise lists is considered to improve readability[196]. More concise information in package leaflets with the shorter model template generally reduced the time needed to find requested information (table 37) and increased the number of correct answers (table 38). Using QRD template 7.3.1 showed an increase in the number of answers 'not found' or' incorrect' in comparison to the model template or QRD template 8 for both long and short text versions in Germany and in England. This is confirmed in a previous study to mainly be due to difficulties in comprehension caused by QRD template 7.3.1 wording[52]. The fact that more correct answers were achieved using QRD template 8 compared to QRD template 7.3.1 indicate that the reworded headings and standard statements have provided better comprehensibility of information. When the long BfArM text version had been read, participants were significantly more of the opinion that 'each subheading clarifies the information contained in the following section' when QRD template 8 had been used rather than QRD template 7.3.1 (table 66). For the short text versions in England, participants also felt significantly better informed from QRD template 8 than QRD template 7.3.1. QRD template 8 therefore does appear to increase comprehensibility of information in comparison to its predecessor.

Two previous studies with the shorter model template, one involving 1105 participants investigating ten package leaflets and another with 192 participants testing six leaflets, confirm its' benefits over the QRD template as found here[52,53]. The study involving 192 participants found on average 18.1 % less time is needed to locate requested information and 15.7 % more information is found or understood when using the model template compared to the QRD template, mainly due to template length and difficulties in comprehensibility[52]. Although the described studies tested QRD templates in German which were current at the time of the research (i.e. year 2000 and 2008), this study provides similar results when comparing the model template to QRD template 7.3.1 and the current QRD template text (excluding the two pharmacovigilance implementations in version 9). The study described in this work is also the first to

demonstrate that the shorter model template has advantages in the English language. In addition, it also showed benefits when using a long package leaflet text as found with the long BfArM sample text (section 4.7).

Increasing the amount of text has previously been shown to decrease ability to locate information thereby discouraging reading of the contents[55]. German participants in the study described in this work favoured leaflets with the model template regardless of whether a long or short text version had been used in terms of motivation to read the leaflet (table 69). This was significant for the short text version in Germany where participants were significantly more motivated to read a leaflet with the model template than with either version of the QRD template demonstrating an advantage of the model template. The length of all three leaflets with the model template was a fact which was commended in the free text section at the end of the questionnaire (table 71). Participants were also satisfied with the scope of information which had been provided as only few mentioned any further aspects which should be included in the package leaflet (table 74). The study of personal opinions of the participants regarding each template revealed that QRD template 8 was always rated better than QRD template 7.3.1 and never worse. However, a further study involving more participants would provide an additional evaluation of opinions on each template version for the package leaflet.

Medical terms should be presented in an understandable way for patients with the lay term and a description first followed by the medical term[38]. The Readability Guideline also suggests using a list with bullet points instead of long paragraphs which can confuse readers[38]. The shortened text versions used in this readability test condensed the information from the BfArM text into a series of bullet points. Although in all leaflets, medical terms had been explained, participants found the content of leaflets with QRD template 7.3.1 the most difficult to understand regardless of whether lists with bullet points or full sentences had been used indicating that the template version influenced readability (table 67).

The order of information contained in the package leaflet and hence listed in the QRD template is stipulated by the Directive 2004/27/EC[24]. The first three sections of the package leaflet thereby contain, in the following order, information on therapeutic group and indication, followed by contraindications and precautions, and then dosage and application errors in section 3. This order of information seems to be acceptable as respondents mostly agreed that all the information which they considered important was contained at the start of the leaflet (table 66). Previous studies have also confirmed that the specified sequence structure meets the needs of both patients and specialists[12]. The section order was suggested due to results of earlier research by German scientists[200] and implicated within the EU with implementation of Directive 2004/27/EC[24].

5.5 Analysis of content, comprehensibility and locatability of information in the QRD template

5.5.1 Comprehension and location of information at the start of the QRD template for the package leaflet

The information box at the start of the QRD template became a feature of the template text in 1998 with the 3rd published edition of the template. It was also a component of the template from the Readability Guideline published in 1998[36]. In the information box the instruction was included not to pass the medicine on to others with similar symptoms as it may harm them. Leaflets with QRD template 7.3.1 and 8 both contained a comparable statement in the information box at the start of the leaflet while the model template investigated had a similar statement in section 5. No clear advantage was seen for either method of presenting the information regarding comprehensibility that it should not be given to others. This indicates that the location of this statement is irrelevant regarding locatability. However, it should also be taken into account that giving medicines to other people is something that generally should not be done which could have affected the number of correct answers.

That the medicine is available on prescription was presented in the information box of leaflets with QRD templates 7.3.1 and 8 and in section 5 of the model template. No significant advantages were seen with regard to the number of correct answers for providing this information in the information box. However, the participants who had read a short text leaflet in Germany with the model template provided significantly more not found answers indicating that location at the start of the leaflet was maybe important in order to ensure that readers can find this information. However, when taking into consideration that prescription status is usually a component of the labelling of the package as described in the 'Blue-box' requirements by the CMDh[179], it could be eliminated in the package leaflet.

The general information usually contained in a box at the start of the QRD template and the Swiss template is not a component of the templates from Australia, New Zealand or the United States. Additionally, this general information contained at the start of the template is not reflected in any European Union or national directives and could therefore be removed from the QRD template, especially as most of the points are repeated elsewhere in the template. The description of what the leaflet is for and why it has been supplied has also been suggested to be superfluous as package leaflets have been provided for a long time within the EU and it can reasonably be assumed that patients know why they are contained in a similar fashion to instructions provided with other products[52]. The sentences contained in the information box of the QRD template 8/9 are enclosed in pointy brackets meaning according to the bracketing convention that they can be completely excluded.

In addition, the information box contains many words which are enclosed in further pointy brackets. For example, for prescription only medicines, strictly applying the optional bracket convention to these further pointy brackets means compressing the applicable 98 words in the information box by up to 40 %[189] if it is not completely excluded. The only point which was deleted at all by MAHs in the study of package leaflets of centralised approved medicines was that the medicine should not be passed on to others when the medicine is only administered by a healthcare professional (table 22). Omission of text phrases in this introductory box should be recommended to the QRD group and marketing authorisation holders in general, and especially in the case that this information is listed elsewhere in the package leaflet. The results from the readability test study described in this work showed that the model template without an information box was not inferior to either QRD template 7.3.1 or 8. A model template without the information box has also been found when used in two further studies not to be inferior to those containing it[52,53]. These results in conjunction with the fact that the information box is not a component of the template in other countries further suggest that this component of the QRD template could be eliminated.

The contents list following the information box in the QRD template also became part of the template text with publication of version 3 in 1998. The annotated QRD templates 8 and 9 state that user testing has indicated that most patients value a contents list[50,56], although this data remains unpublished. The contents list itself is also only of limited use as most package leaflets are not printed as a booklet with page numbers, but rather on a sheet of paper, and the headings provided only state the order of the included main sections but not page numbers as to where to find a particular section. Also, for example, the important subsections contained in section 2 are not listed in the contents list meaning that the reader can not immediately recognise where to locate certain information such as for interactions with other medicines.

The analysis of package leaflets of medicines authorised by a centralised procedure showed that 99 % of the examined leaflets actually contained such as list (table 22). A list of contents is however not a component of all templates which were examined in the study. The Swiss template and United States MedGuides appear to function acceptably without one, and in Australia and New Zealand a list of contents is only required if the leaflet is longer than 4 pages. Use of a model template in two German studies without a contents list also showed no disadvantages in comparison to those containing one[52,53]. The model template used in this study also demonstrated according to the results provided in chapter 4.7 that a clear layout and well emphasised headings are sufficient for navigation. The presence of a contents list to navigate through a booklet appears more meaningful than when used for location of information printed on a single sheet of paper. Eliminating the index in the QRD template or placing it in optional pointy brackets is a suggestion for future versions of the QRD template.

5.5.2 Comprehension and location of information in section 1 of the QRD template for the package leaflet

QRD template 8 and its update - version 9 - suggest the subdivision of section 1 into three paragraphs: invented name, active substances and pharamacotherapeutic group followed by therapeutic indications and then facts on benefits of using the medicine for example under a separate subheading 'How X works'[50]. The use of subheadings in section 1, as recommended in both annotated QRD template versions, is most likely beneficial as providing the pharmacotherapeutic group before the indication has been shown to cause comprehensibility problems[12,53]. This order of information however results from Directive 2001/83/EC[39] and cannot be changed without amendment of this directive.

Additionally naming the active ingredients in section 1 causes a multiple repeat of this information which is presented at the start of the package leaflet and then again in section 6 thereby causing unnecessary increase in the volume of text. Including the active substance name under the name of the medicine at the beginning of the package leaflet is a requirement of Directive 2001/83/EC, Article 59 (1) (a)(i)[39], but '*only where the product contains one active substance and if its name is an invented name*'. This means in many cases that this information is superfluous - a fact which perhaps MAHs and authorities are not aware; therefore, this is not considered in the current QRD template.

The question also arises as to whether patients or users actually interpret this information at the start of the package leaflet, because the name(s) of the active substances presented according to the QRD template, is completely without further context. If the active substances must be included under the medicine name, it would be better to state 'Active substances:' or 'Active substance' (in the case of only one) followed by the names. Furthermore, it has been shown that patients find it sufficient when the names of the active ingredients are simply included before the list of other ingredients[60]. The model template used in this study only contained the name of the active substance in the list of ingredients in section 6, which did not affect significantly the readability test results compared to both QRD template versions independent of which country the package leaflets were readability tested in (table 64).

Only including the active ingredient in section 6 of a model template has also been shown in a previous study to not cause a significant difference between groups with the model template or QRD template 7.3.1 in the percentage of subjects who could correctly name the active substance[52]. Repeating this information therefore appears unnecessary and simply including the active ingredient with the other components at the end of the leaflet is satisfactory. However, even though information on ingredients is considered to not be

the most important, some patients request that this should be included at the start of the leaflet; however, the majority preferred it at the end[12].

The most incorrect answers relating to the active substance name in the readability test study were due to understanding that the pharmaceutical group 'ACE-inhibitor' was the active ingredient, a problem which is due mainly to the wording in the long BfArM sample text version where the first sentence of section 1 reads 'Enal is an ACE-inhibitor'. Inclusion of the sentence 'Enal contains enalapril' in QRD template 8 reduced this problem although the fact that no significant differences were found between template versions in the number of correct answers provided indicates that this sentence in the QRD template 8 is redundant and could be deleted. It should also be discussed in the future, whether mentioning the pharmacotherapeutic group (in this study the term 'ACE-inhibitor') is necessary for the patient, as this is the cause of the problem that the active ingredient is confused with the pharmaceutical group.

Therapeutic indications have been shown to be considered as 'very important' by patients[12,200] who also think that this information should be placed at the beginning of the package leaflet[12]. All participants who had read a leaflet with short text and the model leaflet in both investigated countries could state what the medicine is used to treat (table 41). Wrong answers for leaflets with QRD template 7.3.1 were caused by participants confusing again the pharmaceutical group 'ACE-inhibitor' with the indication, which has also been found in a previous study[52]. This is a problem which resulted from European Directive 2001/83/EC[39] and QRD template 7.3.1 where it was necessary to state this information before the indication. Changing the order of the information in the template could alleviate this problem, although this requires amendment of the European Union ruling.

Addition of a benefit message in section 1 of the leaflet could aid in subjective benefit/risk perception and including positive information in the package leaflet about the potential benefits of taking the medicine may counteract the lists of 'frightening' side effects and other warnings which may dissuade a patient from taking a medicine[101]. An exploratory study showed that insertion of a benefit message had a positive impact on benefit/risk perception as more than 60 % of the people who had read a leaflet with a benefit message perceived greater benefit for the medicine[199]. A further study using textual and numerical benefit information showed that although participants felt that textual benefit information offered an incentive to take the medicine, the numerical benefit information provoked feelings of disbelief and shock as the subjects were surprised that so few people would benefit[201]. Including benefits of the medicine was noted by some participants as information which should additionally be included in the package leaflet. Although the sentence 'Studies show that the benefits of Enal prevail with the correct use' was included at the start of section 4 of the model template and a benefit statement was included in leaflets with QRD

template 8, participants did not have significantly increased belief in the medicines benefits after reading either of these versions in comparison to QRD template 7.3.1 (table 70). Inclusion of a statement about the positive benefit of taking a medication has also been shown to have relatively little effect on judgments, whereas informing people on how to reduce the chances of experiencing side effects was beneficial[202].

5.5.3 Comprehension and location of information in section 2 of the QRD template for the package leaflet

A major change from QRD template 7.3.1 to 8 was altering the heading 'Take special care with X' to 'Warnings and precautions' in QRD template 8 followed by the instruction to talk to a healthcare professional before taking the product[49,51]. The former heading failed to provide any additional precautionary information or actions to take. Participants in this readability test study in England who had received a leaflet with QRD template 7.3.1 often noted that a description of what 'special care' means should be included in the package leaflet (table 74). A report by Andriesen on experience from previous readability tests involving QRD template 7.3.1 described that it had been found that the question as to what 'special care' means often arises with this template version[186]. In this investigation, two questions were included to which the answers were contained in the section 'Take special care with X/Warnings and precautions'. Participants using leaflets with QRD template 7.3.1 consistently provided significantly the most wrong answers in comparison to the other two tested templates as participants had noted that they had to take special care but not known how this should be undertaken i.e. talk to a doctor (tables 46 and 47). This phenomenon has been seen in a previous study[52]. Although the model template used in the readability test in this study provided significantly the most correct answers for information requested in this section for short text versions of the package leaflet, the new heading since QRD template 8 can be seen as providing a significant improvement in comprehensibility in the QRD template in comparison to QRD template 7.3.1, leading to safer use of the medicine. The additional mandatory statement to talk to a doctor or healthcare professional if a specific situation is present before taking the product also provides patients with clear instructions. The annotated template of versions 8 and 9[50] advises MAHs to repeat this advice after each warning/precaution in case of a long-bulleted list - however, this would again lead to an unnecessary increase in the number of words; particularly as the results of both warnings and precautions questions of this study showed in the case of the long and short template versions that such repetition is expendable (tables 46 and 47). Wrong answers regarding what to do in the case of a kidney transplant were caused by participants providing the dosage instructions for reduced kidney function which were given in section 3 rather than the advice in the warnings and precautions section.

A further change from QRD template version 8 was the elimination of the terms 'if you' or 'when' to start the bullet points in the contraindication and warnings/precautions sections. These terms were also not included in the tested model template. The results from this study with QRD template 8 and the model template, and a previous study with the model template[52], show that these words are not necessary and that the information

can be provided simply under each bullet point which moves key messages in close proximity to each bullet point.

Previously QRD template 7.3.1 had included the term ‘hypersensitive’ which was correctly deleted since QRD template 8 as a hypersensitivity, for example, to the excipient lactose does not automatically lead to a contraindication[189]. This must therefore be welcomed as an improvement in the template. However this deletion of the word ‘hypersensitivity’ in the package leaflet and retention of this term in the SmPC leads to an inconsistency between the texts intended for package leaflets and SmPC. This goes against the ruling in Article 59 of Directive 2001/83/EC as both package leaflet and SmPC must be in accordance with each other[39].

The analysis of package leaflets downloaded from the EMA website revealed that not all MAHs were of the opinion that ‘hypersensitivity’ should be deleted and over 20 % of the examined leaflets in the second and third download with QRD template 8 or 9 still retained both terms. In the third download, there was also a reduction in the percent of package leaflets which only used the term ‘allergic’ in comparison to the second download. The use of both terms, and the previously mentioned reduction in use of the term ‘allergic’, maybe due to the fact that the SmPC in QRD template versions 8/9 still retains the term hypersensitivity and MAHs want to conform to Directive 2001/83/EC and retain conformity between the package leaflet and the SmPC.

Excipients mentioned in the Excipients Guideline[94] are not only listed at the end of the leaflet, but additionally under a separate heading at the end of section 2 which was the longest heading in QRD template 7.3.1. The wording of this heading, ‘Important information about some of the ingredients of X’ has previously been shown that although it attracts attention due to its length, to cause confusion[186] and has led to the belief that the name of the active substance is described here[52]. It was recommended that as this section often only contains one ingredient such as lactose, thereby making it interesting only to those who are hypersensitive to lactose, that it should be changed to ‘X contains lactose’. Since QRD template 8, this change has been implicated, but the results of this study show that this did not increase the participants understanding of whether they can take the medicine if they are allergic to lactose (table 44). In fact, the question ‘Can you take this medicine if you are allergic to lactose?’ showed the fewest correct answers in the study. In general, this tested information was usually misunderstood for leaflets with QRD template 7.3.1 or 8 and ‘not found’ for leaflets with the model template. The warning as stipulated by the Excipients Guideline was mostly the cause of the comprehensibility problems[94]. It was commonly thought, that the medicine could be taken if the doctor was consulted, therefore, the wording for this phrase should perhaps be reconsidered. The model template demonstrated that an extra subheading for lactose and the warning

statement are perhaps unnecessary in future versions of the QRD template. A further alternative would therefore be to delete the extra excipients warning and statement at the end of section 2 and integrate the information into the paragraph describing warnings and precautions.

The heading in the QRD template regarding taking the medicine with food and drink was found in readability studies by Andriesen involving QRD template 7 to cause confusion as readers believe this section will tell them when to take their medication; before or after a meal, with or without water[186]. It is however explicitly mentioned in the explanatory text in QRD template 8 that such information should be listed in section 3[56]. Since publication of QRD template 8, the term alcohol can be optionally added to the 'Taking X with food and drink' heading. This caused a significant reduction in the number of not found answers for leaflets with the long text version regarding taking the medicine with alcohol (table 50). However, the results also demonstrate that use of the additional term 'alcohol' in package leaflets with QRD template 8 did not cause it to be superior to the leaflets without this term. The short, clear subheading used in the model template again provided evidence that a good heading/subheading does not have to be long to increase comprehensibility or locatability of information, but rather that the information contained under a specific heading/subheading must be comprehensible.

The heading 'Driving and using machines' was identical in all template versions of the leaflet. The volume of text under this heading may have influenced the fact that participants with the long BfArM text had more difficulty in finding a reason why their ability to drive maybe affected. This result is similar to that of the previous question relating to alcohol (table 45). Common incorrect answers relating to driving were caused by the BfArM text itself rather than the template as subjects had simply written 'start of treatment' or 'dose increase' which although not false is not a reason why ability to drive may be reduced, but were explanations contained in the section.

Information on pregnancy and breast-feeding was provided in model template leaflets in the special warnings or contraindications sections only. The percentages of correct answers to two questions relating either to use during pregnancy or breast-feeding showed no significant advantage of any template version independent of whether this information was repeated in a separate QRD template paragraph or not (tables 42 and 43). As there were no significant differences found to the model template, integrating this information into the existing section can be recommended which has been identified in previous studies[52,53,60]. The investigation into templates used in other countries also revealed that the Australian CMI template contains no separate pregnancy, breast-feeding or fertility sections but information regarding these situations is contained within the contraindication or warnings section which was also shown to be sufficient according to the results provided in tables 42 and 43.

Description of interactions between medicines in the package leaflet are considered by patients to be 'very important' although the location of these interactions should be placed somewhere near the middle of the package leaflet[12,200]. In package leaflets with the model template or QRD template 7.3.1, medicine name and a description of its use were separated by a colon, whereas for QRD template 8 a description of the medicines actions was closed in brackets according to the recommendations in the annotated template version. This was found not to affect the number of correct answers, therefore strictly abiding by the convention in QRD templates version 8/9 is unfounded and not necessary. Participants who had read the long BfArM version of the leaflet found it difficult to locate a medicine used to treat heart rhythm disorders which can influence Enal (table 48), a problem which was probably due to the volume of text in the interaction section reducing the chance of finding information, which has been seen previously[55]. A negative influence of the template wording is unlikely as the short text version in both languages showed better results. Conform to the BfArM sample text, the name of the medicine used to treat heart rhythm disorders was only in the section 'Take special care/warnings and precautions' rather than in 'Taking other medicines/Other medicines and Enal' thereby increasing difficulty in finding as participants probably expected such information in the interaction section. This result again demonstrates the importance of locating information under the relevant heading/subheading, and that an additional repeat of information regarding interactions should not be mentioned in the warnings and precautions section, as patients do not expect to find such information at this location.

A question was also used in the study in which participants had to identify what they should do if they were already taking a medicine to reduce blood sugar levels (table 49). This information was always contained in the interaction section of the package leaflet. No significant differences were found between any template versions and therefore it was shown again that alternative use of colons instead of brackets did not affect the number of correct answers regarding medicine interactions. The number of correct answers provided for all template versions with the long BfArM text was generally much higher than for the question regarding interactions with a medicine to treat heart rhythm disorders, again demonstrating that it is vital that information is always contained in the appropriate section to aid locatability.

QRD template 8 implemented an extra subheading in section 2 for 'children and adolescents' for when a medicine is indicated in children and this subheading was therefore used in leaflets with this template version for this study. All leaflets contained information regarding treatment in children in the dosage section (section 3). The long versions of the BfArM text also always provided information in section 2 of the package leaflet as this was present in the sample text from BfArM. The results provided in table 51 show that this heading is superfluous regarding finding what indication the medicine is used for in children

as there were no significant differences found between leaflets which contained this subheading in section 2, and those which only contained information in section 3. A single subheading is sufficient for finding this information as long as all relevant information is summarised and present at a single location.

This heading however when provided as 'children and adolescents' is rather ambiguous as no statement is made on which age ranges are affected. Addition of ages in the heading, as was used in all package leaflets with the model template, would be more helpful as the user can judge who is affected by the content of the section. Addition of the term 'adolescent' is also superfluous according to the definition of children by the EMA where children are defined as 'people from birth up to 18 years of age' meaning that adolescents also fall within this category[203].

5.5.4 Comprehension and location of information in section 3 of the QRD template for the package leaflet

Clear and precise dosage instructions are essential to a patient for correctly using medicines. Dosage instructions and application error tips are considered by patients to be 'very important' in the package leaflet[12]. However, whereas patients consider that dosage instructions should be present at the start of the leaflet, application errors should be placed nearer the end[12,200]. Dosage instructions given in active substance quantities rather than number of tablets have been shown to cause difficulties in patient understanding[53] with up to 90 % of patients not understanding dosage instructions in milligrams of active substance[204]. In this study, the short text versions of the leaflet described the starting dose in amount of tablets while the long text version from BfArM gave the dose in milligrams of active substance. The results in this research project (table 52) are supported by the mentioned study as participants found describing the starting dose more difficult when the quantity of active substance was provided in the package leaflet, as more correct answers were given with the short text leaflet versions when compared to the long BfArM text versions. Although both milligrams and number of tablets were considered as correct answers, participants who had read the long BfArM texts always attempted to provide their answers in milligrams rather than the equivalent number of tablets. Therefore the QRD template should enforce that only numbers or the volume of a ready to use medicine, such as number of tablets, are described rather than active substance amount.

The subheading 'duration of use' was included in all package leaflets except for the long text version with QRD template 7.3.1 as the BfArM sample text did not include it. This probably accounted for the significant difference between the model template and QRD 7.3.1 with regard to the number of not found answers (table 56). The annotated version of the QRD template 9 suggests including specific information with regard to duration of treatment which should be based on section 4.2 of the SmPC but no subheading is recommended. This study however showed that a subheading is beneficial. The shorter leaflet versions

provided more correct answers than the long BfArM leaflet versions as although in each leaflet participants were told that duration of use is determined by the doctor, the BfArM text for enalapril additionally included the fact that the medicine is usually for long term use. Participants had therefore noted that the medicine is for long term use but not correctly that the duration of use is determined by a doctor. Statements such as '*längere Anwendung*' (long term use) have been shown in a previous study to be non-quantifiable wording which does not aid the patient in estimating the correct time interval for taking the medicine or importance of the information[60], which is also seen in the results of this study.

The QRD templates 7.3.1 and 8/9 include a subheading in section three for forgotten use of the medicine under which the standard statement 'do not take a double dose to make up for a forgotten dose' is contained[48,49,51]. The model template included the additional information 'but continue taking the medicine as prescribed'. The statement in the QRD template seems not to provide clear advice for the patient as the most correct answers on what to do in case of a forgotten dose came from the model template (table 53), indicating that the sentence in the QRD template should possibly be supplemented with additional information.

The slightly different subheading wording between template versions regarding information on overdose were found to not cause any significant differences in the number of correct, wrong or not found answers between template versions, showing that each template version was equivalent (table 54). QRD template 7.3.1 and 8 both contained the same heading in the long BfArM text versions for when a patient wants to stop taking the medicine. There is therefore no explanation for the significantly more correct answers for QRD template 8 in comparison to QRD template 7.3.1 (table 55).

5.5.5 Comprehension and location of information in section 4 of the QRD template for the package leaflet

Informing users about the risk of side effects from their medicines is vital if they are to be able to make informed decisions about their medicine taking[183]. However, studies have shown that patients who have read the package leaflet are more likely to relate health problems which could be side effects to the medicine taken and stop taking it[205]. Although this phenomena is not always observed[5,206].

The first Readability Guideline from 1998[36] described how the frequency of side effects could be presented using five verbal descriptors accompanied by a defined numerical rate[36]. Testing of these adjectives 'very common', 'common', 'uncommon', 'rare' and 'very rare' has however shown that they lead to a significant over estimation of risk[207], as well as significantly reduced intention to comply[208]. Use of just the verbal descriptors has been shown to also cause considerably higher estimated side effect risk than when a comparable numerical descriptor in the form of a percentage without an adjective is given[209].

A study involving the use of verbal descriptors, percentages and natural frequencies (absolute frequencies which result from observing cases) further supported these results as verbal descriptors alone led to significantly higher estimations of risk compared to the two other formats[210].

It is however not only laymen who have problems understanding side effect frequencies regardless of how they are presented, verbal descriptors, numerical or combined, as discussed in the previous paragraph. A study in Germany in 2013 involving 1000 doctors, pharmacists and lawyers tested whether 20 verbal definitions of probability could be interpreted numerically by providing the percentage value[211]. The answers provided were compared to the theoretical values in the official BfArM published guidelines from November 2006, for example, '*Häufig: weniger als 1 von 10, aber mehr als 1 von 100 Behandelten'*[118] (common: less than 1 in 10, but more than 1 in 100 patients). Few of the participants could allocate the correct percentage to the terms '*Häufig*' (common), '*Gelegentlich*' (uncommon) or '*Selten*' (rare) and it was shown that the possibly of overestimation of the probabilities of side effects is present in groups of specialists in medicine-related fields[211]. The authors concluded that the definitions of frequencies provided by BfArM do not correspond to the commonplace use of the terms.

A study which investigated the use of three formats for communicating the risk of side effects to patients found that the use of combined descriptors such as 'common (affects less than 1 in 10 people)' was not unequivocally superior to absolute frequency alone (e.g. less than 1 in 10 people) and that verbal descriptors (e.g. common) showed deficiencies for conveying side effect risk[212]. Participants who had received information in the absolute frequency format were more satisfied with the information than the verbal format. A further study also involving three formats for communicating risk showed that the three different presentations did not differ in their effect on participants interpretations[213]. The three risk expressions tested were: percentages e.g. affects 25 % of people', frequencies e.g. affects 1 in 4 people' and combined e.g. affects 1 in 4 people (25 %). The preferred format was however the combined frequency and percentage risk expression e.g. affects 1 in 4 people (25 %)[213].

The green explanatory text in the annotated QRD templates 8 and 9 states that a combination of verbal terms and numerical data should be used to describe the frequency of side effects, and that user testing has shown that double sided expressions such as 'affects more than 1 in 100 but less than 1 in 10' (from the Readability Guideline published in 1998) are not well understood[56]. However, data which support this opinion has not been published by the QRD group. In the current SmPC a double-sided frequency convention is recommended e.g. 'common (≥ 1/100 to < 1/10)'[67] while the annotated versions of QRD templates 8 and 9 use a frequency explanation which is closed on one side for the package leaflet e.g. 'common, may affect up to 1 in 10 people'[48]. The side effect frequency explanations are thereby also

discrepant with regards to ruling in Article 59 of Directive 2001/83/EC as both package leaflet and SmPC must be in accordance with each other[39]. This point alone requires that the current QRD template must be amended in the side effect frequency explanation.

Before publication of QRD template 8, the recommended frequency explanation was that published in 2007 by BfArM[120]/EMA[182] e.g. 'Common: affects 1 to 10 per 100 users'. The analysis of package leaflets downloaded from the EMA website showed that the method of describing frequencies of side effects changed during the examined time period. Initially, the description type from the BfArM recommendation[120]/EMA report[182] was greatly favoured by MAHs followed by that since QRD template 8[50] ('Common: May occur in up to 1 in 10 users'). Although the frequency description from the BfArM/EMA remained the most commonly used in the second download, the number of leaflets using this method decreased while the number of leaflets with the QRD template 8/9 recommendation increased (table 28) indicating that MAHs followed the recommendations provided by the QRD template.

In the readability test in this study, three methods of describing side effects were used. The model template used the recommendations from 2007 made by BfArM[120] and the EMA[182]. These side effect frequency explanations are in compliance with those recommended for the SmPC and were developed and successfully tested in a readability test study involving 1105 participants[53]. Leaflets with QRD template 7.3.1 used the verbal and numerical text published in 1998 in the first Readability Guideline[36], while leaflets with QRD template 8 used the descriptors published in the annotated template since QRD template 8 - a side effect frequency explanation for which no evidence has been provided to confirm that it is the most optimal version. It was found in this study that the double sided frequency explanations used in QRD template 7.3.1 leaflets caused comprehensibility problems. It was however not found that using double sided expressions such as that in the model template led to reduced understanding as stated in the annotated QRD templates 8 and 9[50,56].

When participants in this study were asked to identify in which frequency group a side effect belongs if it affects 5 in 100 people, QRD template 8 frequency explanations showed the worst comprehensibility. However, an analysis of the wrong answers provided by participants showed that for both QRD template 7.3.1 and 8, the main problem was that the provided numerical explanation could not be assigned to the correct frequency group. For QRD template 7.3.1 this was maybe because the frequency explanation was too long and complicated which led to comprehensibility problems. And for QRD template 8, although the frequency explanations were short, it was poorly comprehensible which mostly led to an undervaluation of the frequency but also in some cases to an overvaluation. The results of the PAINT3 study investigating 295 package leaflets with 5091 participants back-up these findings relating to inferiority of the current

QRD template frequency explanation. In the described German study, the EMA side effect frequency explanations from 2007 used in the model template were found to have a 10 % higher comprehensibility rate than that in the QRD template since version 8[189]. The presented results from the PAINT3 study and this research indicate that the QRD group is wrong in its general negative opinion relating to using double-sided frequency expressions. However, it can be postulated that the frequency explanations in the current QRD annotated template are probably better comprehensible than those published in the Readability Guideline from 1998, as it is shorter with less complex phrasing[52].

When participants were asked to write down in numbers 'How many people are affected by a side effect if it is rare?', the participants using the model template and QRD template 8 frequency explanations always provided more correct answers than when using the QRD template 7.3.1 version, although these differences were not significant (table 58). The results in table 58 therefore do not demonstrate that the frequency explanations used in QRD template 7.3.1 from the Readability Guideline published in 1998 was inferior to the other two description methods in this study, or that double-sided expressions were less comprehensible as shown by results obtained from participants using the model template. The non-significant result may be caused by a lower number of participants in comparison to the PAINT3 study by Fuchs et al. published in 2012 whereby 5091 participants were involved[52]. In the PAINT3 study, the double-sided explanations such as 'common, affects 1 to 10 per 100 users' showed a significantly higher comprehensibility rate than the QRD template explanation valid since version 8.

As shown in section 4.7.9 and table 59 of this study, the current QRD template side effect frequency explanation often leads to an overestimation of side effect frequency by up to a factor of 10, although overestimation of risk has been found regardless of the manner of presentation[214]. When subjects were asked 'How many people are affected by a side effect if it is rare?', the correct answer would be that it affects 1 to 10 in 10,000 people, however when participants had read a leaflet with QRD template 8/9 side effect frequency explanations, nearly all of them believed that a rare side effect generally affected 1 in 1000 people which is the maximum frequency for a rare side effect.

The way of presenting the frequencies of side effects (either as a table at the start of section 4 or as part of the list) was found in this study not to produce any significant differences between template versions in the ability of participants to comprehend and locate how many people were affected by a side effect if it was rare (table 58). Incorporating the frequency descriptions of side effects into the list of side effects rather than using a table at the start of section 4 for the frequencies however reduces the space needed to print this section of the package leaflet. Also, using side effect frequencies as subheadings and subsequently listing the corresponding side effects brings both in near proximity making it easier for the

user to read which side effects are listed with a certain frequency. This change in frequency description has been assessed by other authors as positive[189]. Furthermore, the table for side effects was considered by participants as being unnecessary as it was an element which some participants wished to delete in the package leaflet (table 73).

The Readability Guideline from 1998[36] suggested dividing side effects into 'serious' where medical advice should be sought immediately, and 'less serious' which is also recommended since QRD template 9. The wording used is important as testing of the terms 'immediately' and 'as soon as possible' has shown not to be interpreted differently, although the meaning of the two terms is very different[215]. Some side effects such as severe allergic reactions require 'immediate' medical attention, whereas a doctor can be consulted at the patients' convenience ('as soon as possible') for other side effects, indicating that clearly worded statements and actions to be taken are vital. The side effect section was structured differently in this study for each version of the leaflet whereby leaflets with QRD template 8 followed template recommendations and presented the most serious side effects first, the model template had serious side effects printed in bold and leaflets with QRD template 7.3.1 listed 'countermeasures' at the end of section 4 for serious side effects. When participants in this study were asked to locate a serious side effect where they should immediately contact their doctor, there were no significant differences between the number of correct or wrong answers provided between template versions. However, for the long BfArM text versions, the model template provided significantly more not found answers that either QRD template, indicating that using bold type in the model template was inferior to listing severe side effects first which is suggested in the QRD template since version 8, or having a separate section for countermeasures (table 62).

Knowing how to take appropriate actions is important if any side effects should occur, but the wording in QRD template 7.3.1 led many patients in this study to believe that a healthcare professional should only be contacted 'If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet.' This has also been seen in other studies[52,53]. QRD template 8 provided the most correct answers (table 61). Generally recommending contacting a doctor if side effects occur reduced misunderstanding and can therefore be welcomed as an improvement.

The new subheading in section 4 of QRD template 9 'Reporting of side effects'[48] and the mandatory text whereby patients are actively encouraged to report any occurring side effects was caused by the pharmacovigilance legislation implemented in 2013[42]. The text extension cannot be seen as positive as the word count of mandatory text in the side effect section of QRD template 9 is increased by three times in comparison to its predecessor and it cannot be excluded that this will reduce the usability of the provided instructions[48,49]. The supposition that medical laymen can differentiate between side effects caused by a

particular medicine rather than symptoms caused by other factors such as the particular condition itself must also be considered critically[216]. Moreover, using package leaflets for other purposes such as reporting side effects deviates from their intended function of informing patients on proper use of their medication.

5.5.6 Comprehension and location of information in section 5 of the QRD template for the package leaflet

Storage information was always contained under the same heading in section 5 of the leaflet for all versions. This information is considered by patients to be 'important' and it is considered that it should be located at the end of the leaflet[12,200]. The shorter message contained in the model template regarding keeping the medication inaccessible to children proved sufficient as no significant differences were seen between template versions (table 63).

5.5.7 Comprehension and location of information in section 6 of the QRD template for the package leaflet

In the European Union, the package leaflet is intended for use by the patient whereas the SmPC is designated for specialist use. This separation of medicinal information was intended to make the package leaflet more patient-orientated. However, since publication of QRD template version 5 a separate heading was provided at the end of section 6 for information for healthcare professionals. Around 24 % of leaflets from each download of package leaflets from the EMA website contained information for healthcare professionals, which in some cases accounted for over 50 % of the total words (table 26). Although it has been shown that specialists use patient information as much as patients[12], this study demonstrated that the volume of text is greatly increased by this information. In view of the fact that a SmPC is available for professionals, care should be taken by MAHs in the amount of professional information which is included in the patient leaflet.

The QRD template for centralised procedures makes provision for a list of 30 names and addresses of local MAH representatives. Although inclusion of this list is non-compulsory, over 80 % of the examined leaflets in each download of package leaflets from the EMA website contained this list which contributed to up to 33.6 % of the total text volume. According to the readability test results provided in table 73, this list was the most frequent aspect of the package leaflet which participants would delete. As increasing the number of words is a major factor in decreasing patients' motivation to read the leaflet and their ability to locate information[55], omission of this list should supported, especially as it does not offer any medicine specific information, contributes to the text volume and is little importance for patients or healthcare professionals. Additionally, limitations of spoken languages make it unlikely that patients would contact

foreign representatives, and QRD template version 3 also does not recommend such a list for non-centralised approved medicines. Furthermore, this information can be reduced to only the relevant local representative and not the entire list of local representatives. This change will be implemented in a revised version of the QRD template which will include this guidance (personal communication, EMA 2014).

5.5.8 Comprehension and location of information regarding tablet divisibility

When specialists were asked what information should be contained in a package leaflet, it was stated that information outlining tablet divisibility should always be present[12]. Divisibility can be described verbally or by using a pictogram or both. Patients are often presented with a tablet with a score line which could cause confusion as a score line does not always mean that a tablet can be divided into equal doses but rather than two halves are easier to swallow than a whole. The annotated version of the QRD template 8 took this into account and included three optional statements regarding divisibility.

As QRD template 8 included the optional statement 'this tablet can be divided into equal doses' this sentence was included in package leaflets used in this readability test study with this template. Leaflets with the shortened text version all contained a picture of the tablet being divided which probably accounted for the fact that over 97 % of participants could answer the question correctly as to whether the tablet could be divided. With the long BfArM text version, leaflets with QRD template 8 provided significantly the most correct answers showing that the statement regarding divisibility is essential (table 65). The other two leaflets with the long BfArM text version contained neither statement nor picture regarding tablet divisibility. The picture showed better results in the location and understanding of the provided information in comparison to the statement as in leaflets with QRD template 8, as was demonstrated by the results from the short leaflet versions.

5.5.9 Effects of demographic factors on participants ability to comprehend and locate information

It has been shown that elderly people and those with a low level of academic education have particular difficulty in finding and understanding medical information in package leaflets with older readers also needing more time to locate information[217]. In the study described in this work, readers in Germany who were older than 60 needed the longest time to answer the questionnaire in the readability test whether a longer or shorter text had been read with youngest participants being the fastest (table 75). In England however, participants who were over 60 were fastest reading the short leaflet. Influences of the age structure present in the English subject group may account for this result. A further similar study has shown that as age increased, that the time taken to locate and provide requested information was increased[53].

Participants who had only completed education to the 8th class provided the least correct answers although this was not significant (table 77). For all other education levels no significant differences were found which indicated that a higher education level had led to better understanding of the leaflet. The number of medicines participants took each day also did not influence the number of correct answers provided (table 76) as has been previously seen in a similar study[53].

5.6 Global aspects relating to the QRD template

The analysis of the number of words in the QRD template from the initial publication to the present day showed that both the minimum and maximum number of words contained in the template has steadily increased which thereby plays a role in the increasing text volume in package leaflets. The QRD template 9 published in March 2013 showed a further text increase due to additional text elements based on the new EU pharmacovigilance legislation which is intended to increase patient safety when using medicines[24,25]. The analysis of package leaflets available on the EMA website for centralised approved medicines showed that pharmaceutical companies use up to 67.3 % the QRD template 9 text (565 of the possible maximum 840 words in this template version). As the maximum possible number of words contained in each version of the QRD template was never used in the examined package leaflets, it would seem that MAHs often follow, at least partially, the bracketing convention and do not use the QRD template in its entirety. Chapter 4.6.3 of this research shows that between an average of 19.7 % and 21.5 % of the text in each leaflet was caused by the QRD template depending on template version, with implementation of the actual template version 9 causing the greatest average percent of template words (tables 25 and 26). The results show that with each new edition of the QRD template the average number of words in the package leaflet caused by this template increased by more than 10 %. However, both patients and healthcare professionals strongly favour more concise package leaflets[1,12] and it has also been shown that increasing the number of words used in package leaflets significantly decreases patients', motivation to read the package leaflet, reduces trust in using the medicine plus the ability to locate the provided information is impeded[55,218]. When assessing readability of package leaflets, a correlation has been found between the number of words and poor or good readability. Package leaflets which motivated patients to read them, increased confidence in the medicine and with good readability regarding ease of location of information were found to have less than 1500 words[218]. This again shows the importance of keeping package leaflets as concise as possible which must also take the length of the QRD template itself into consideration.

The latest versions of the template have led to the introduction of the optional use of the terms 'patient' or 'user' at the top of the leaflet. This choice is not necessary advantageous as the term 'user' could simply be written rather than trying to take into account everybody who might read the leaflet. A further fault of the template from version 3 onwards in English is the heading at the top of the template. The term

'Package leaflet' could be unclear as in the UK the term 'Patient information leaflet' is commonly used[101]. Implementation of pharmacovigilance legislation in QRD template version 9 caused the introduction of a black inverted triangle to identify products which are subject to additional monitoring[43]. The presence however of a black symbol and statement that the medicine is 'subject to additional monitoring' may cause patients to be put off taking a medicine as they consider it unsafe[216] and cannot be assessed as positive.

Additional use of other optional terms has been introduced in the most recent versions of the template for example 'nurse' in some sections where previously only the terms 'doctor and/or pharmacist' were listed, 'alcohol' in the subheading of the section for interactions with food and drink, and 'fertility' in the section subheading for pregnancy and breast-feeding. Use of these additional terms further contributes to the text volume. Information on fertility does also not have to be described for each medicine according to Directive 2001/81/EC Article 59, 1 (c)[39]. The study of the package leaflets for centralised approved medicines showed that too little thought is frequently given by MAHs and agencies when using the optional terms 'fertility' in the heading for pregnancy and breast-feeding and 'alcohol' in the section for interactions with food and drink (section 4.6.8). The situation was seen that over 25 % of package leaflets which used the term 'fertility' in the subheading of the second and third downloads contained no information regarding fertility and around 10 % of package leaflets in the second and third downloads which used the term alcohol in the subheading had no information on alcohol, meaning that these terms were superfluous, a fact which maybe MAHs should be made aware of. A further example of suboptimal use of the template was seen regarding the optional standard sentence present under the subheading 'Pregnancy and breast-feeding'. Although in the minority, several package leaflets contained the wording for this sentence from both template versions 7 and 8/9, thereby causing an unnecessary increase in text in this section, perhaps as deletion of the previous text version had been overseen. The analysis of package leaflets for centralised procedures also demonstrated that a large number of package leaflets were only partially adapted to the QRD template, for example, with regard to the standard warning statement for interactions with other medicines. The situation was seen in download three, that 21.4 % of the package leaflets with QRD template 8/9 still retained the statement from QRD template 7.

The QRD template contains numerous repetitions although this is advised against in the readability guideline[38] as it leads to text redundancy and causes unnecessary increases in text volume. For example, the name of the active ingredient is repeated three times in the template since publication of QRD template 8, and the information that a patient must contact a doctor if side effects occur is contained in the information box at the start of the leaflet and at the end of section 4 with identical wording. The results of the readability test in this study showed that repeating the name of the active ingredient is redundant in the

template and it is sufficient to simply list it along with the list of other ingredients. This multiple repeat should therefore also be eliminated in the template. The model template used in this study contained no information box and the advice sentence if side effects occur was contained at the end of section 4. QRD template 8 provided significantly more correct answers than the model template for short text versions in England and the long BfArM text versions (table 61), however the wording used for each template differed which may have led to the differing comprehensibility rather than the fact that the information was not contained at the start of leaflets with the model template. A separate section for pregnancy and breast-feeding also causes a repeat of information and as the model template without a separate section showed, integration of this information into contraindications or warnings and precautions is sufficient, thereby eliminating a further repetition of information.

5.7 Summary of advantages/disadvantages/significant differences between templates

5.7.1 Comparison of QRD template 7.3.1 and 8

A comparison of the results from the readability test revealed that package leaflets with QRD template 8 was mostly superior to those with QRD template 7.3.1 in terms of comprehensibility for long and short text versions in both languages (table 78) showing that QRD template 8 had improved readability in comparison to its predecessor. More correct answers were provided with QRD template 8 which could be influenced not only by the fact that the information was more comprehensible, but that the increased comprehensibility made it easier to find. The subheading 'warnings and precautions' in QRD template 8 rather than 'take special care with X' in QRD template 7.3.1 led to better comprehensibility and locatability of how to act in the case of a kidney transplant or when a dental operation is needed. It was also demonstrated that QRD template 8 provided better comprehensibility than QRD template 7.3.1 in section 3 of the package leaflets.

QRD template 7.3.1 used a table preceding the list of side effects to describe the frequencies while QRD template 8 describes the frequency of side effects as part of the list as subheadings. This method is space saving and brings the respective side effect in close proximity to the frequency[189]. The description method of side effect frequencies from QRD template 7.3.1 was found to be superior to that from QRD template 8 in terms of comprehensibility for all versions of the package leaflet in both languages. Presenting the side effect frequencies in a table as in QRD template 7.3.1 perhaps makes this information more visible which led to more found answers than with QRD template 8.

The statement on how to act if side effects occur from QRD template 8 was more comprehensible and easier to find than that from QRD template 7.3.1 especially in short versions of the leaflet. The large number of wrong answers provided by participants who had read versions of the leaflets with QRD template 7.3.1 were caused by misunderstanding the wording in QRD template 7.3.1 which has also been found in a previous study[53].

The participants' opinions in England for short versions of the leaflet showed that it was considered that the subheadings in QRD template 8 were more comprehensible than those in QRD template 7.3.1 and they were more satisfied with the information provided in package leaflets with QRD template 8. Participants who had read long BfArM versions of the package leaflet felt that leaflets with QRD template 8 had provided the better instructions for using the medicine. These results on the subjective opinions of the participants also demonstrate the superiority in terms of patient satisfaction with QRD template 8.

Table 78: Significant differences found in the readability test between QRD template 7.3.1 and QRD template 8

Item	Subitem	Significant advantage for		Which text versions showed significant differences			Comment	Reference
		QRD template 7.3.1	QRD template 8	EN - short text	DE - short text	DE - long BfArM text		
Total of provided answers	Total result		x	x	x	x	QRD template 8 more correct answers due to better comprehensibility	Table 38 Appendix 13
	Comprehensibility		x	x	x	x	QRD template 8 less wrong answers	Table 38 Appendix 13
Package leaflet section 2	Better understanding and location of warnings and precautions		x	x	x	x	QRD template 8 more correct and less wrong actions in the case of a kidney transplant*	Table 47 Appendices 14, 15, 16, 17, 18, 19
			x			x	QRD template 8 less not found actions in the case of a kidney transplant	Table 47 Appendix 22
			x	x	x		QRD template 8 more correct actions if dental operation needed	Table 46 Appendices 14, 15
			x	x	x		QRD template 8 less wrong actions if dental operation needed	Table 46 Appendices 17, 18

Item	Subitem	Significant advantage for		Which text versions showed significant differences			Comment	Reference
		QRD template 7.3.1	QRD template 8	EN - short text	DE - short text	DE - long BfArM text		
	Better location of information on interactions with food and drinks		x			x	QRD template 8 less not found answers what should be done with regard to drinking alcohol when taking the medicine	Table 50 Appendix 23
Package leaflet section 3	Better location of dosage instruction		x			x	QRD template 8 less not found answers for starting dose to be taken	Table 52 Appendix 22
	Better method of use result		x			x	QRD template 8 more correct answers for whether the tablet can be divided	Table 65 Appendix 16
	Better results for what to do if desired to stop treatment		x			x	QRD template 8 more correct answers on how to act if treatment should be stopped	Table 55 Appendix 16
Package leaflet section 4	Better results understanding side effect frequencies	x		x	x	x	QRD template 7.3.1 more correct answers for 'In which of the side effect frequency groups does the following frequency: 'affects 5 in 100 people' belong?'	Table 60 Appendices 14, 15, 16

Item	Subitem	Significant advantage for		Which text versions showed significant differences			Comment	Reference
		QRD template 7.3.1	QRD template 8	EN - short text	DE - short text	DE - long BfArM text		
	Better results understanding side effect frequencies	x			x	x	QRD template 7.3.1 less wrong answers for ‘in which of the side effect frequency groups does the following frequency: ‘affects 5 in 100 people’ belong?’	Table 60 Appendices 18, 19
	Better locatability of side effect frequencies	x		x	x	x	QRD template 7.3.1 less not found answers for ‘in which of the side effect frequency groups does the following frequency: ‘affects 5 in 100 people’ belong?’	Table 60 Appendices 20, 21, 23
	Better results of how to act in the case of side effects occurring		x	x			QRD template 8 more correct answers on how to act if a side effect occurs	Table 61 Appendix 14
	Better results of how to act in the case of side effects occurring		x	x	x		QRD template 8 less wrong answers on how to act if a side effect occurs	Table 61 Appendices 17, 18

Item	Subitem	Significant advantage for		Which text versions showed significant differences			Comment	Reference
		QRD template 7.3.1	QRD template 8	EN - short text	DE - short text	DE - long BfArM text		
	Better locatability of how to act in the case of side effects occurring		x	x			QRD template 8 less not found answers on how to act if a side effect occurs	Table 61 Appendix 20
	Better locatability of the frequency of a specific side effect		x			x	QRD template 8 more correct and less wrong answers for 'how frequent is the side effect 'hair loss'?'*	Table 57 Appendices 16, 19
Partici-pants opinion	Subheading wording		x			x	QRD template 8 more favoured for statement 'each subheading clarifies the information contained in the following section'	Table 66
	Comprehensibility		x	x			QRD template 8 more favoured for statement 'the content of this package leaflet was easy to understand'	Table 67

Item	Subitem	Significant advantage for		Which text versions showed significant differences			Comment	Reference
		QRD template 7.3.1	**QRD template 8**	**EN - short text**	**DE - short text**	**DE - long BfArM text**		
	Satisfaction with provided information		x	x			QRD template 8 more favoured for statement 'I feel well informed from the information contained within this package leaflet'	Table 68
	Satisfaction with provided information		x			x	QRD template 8 more favoured for statement 'this package leaflet provided all the instructions I needed to use the medicine'	Table 68
Number of siginif-icant advantages for:	QRD template 7.3.1	-		2	3	3	Total result: QRD template 8 is superior to QRD template 7.3.1 with the exception of the side effect frequency explanation	-
	QRD template 8			11	7	13		

EN = English, DE = German

* If significantly more correct and less wrong answers were found, this result was counted twice

5.7.2 Comparison of model template and QRD template 8

Comparing the results of the readability test between QRD template 8 and the model template revealed that the model template was more comprehensible in terms of providing more total correct answers and less wrong answers than QRD template 8 for short text versions in both languages (table 79). However, the model template was significantly better than the QRD template 8 in terms of the time needed to find the requested information for long BfArM text versions. Package leaflets using the model template contained more than 1000 words less than the package leaflets with the QRD templates which most likely accounted for this result. Information was also presented under clearer, shorter headings.

Further advantages of the model template were also seen several times with regard to understanding warnings and precautions located in section 2 of the package leaflet. However, QRD template 8 was superior once to the model template in terms of locatability of information for long BfArM text versions with respect to how to act in the case of a kidney transplant.

When participants were asked in which side effect frequency group the frequency 'affects 5 in 100 people' belongs, the comprehensibility and locatability of this information was superior for the model template compared to QRD template 8 for all package leaflet versions as already discussed in section 5.5.5. The description method of frequencies from QRD template 8 has previously been shown to be less comprehensible[189] and causes an important overestimation of side effect frequency.

The sentence from QRD template 8 instructing participants on how to act in the case of side effects occurring was superior to that from the model template in terms of comprehensibility and locatability. The QRD template 8/9 requests that most serious side effects are listed first corresponding to the recommendations of the Readability Guideline from 2009[38]. Describing most serious side effects first showed an advantage for the QRD template 8 in comparison to the model template for long BfArM text versions. Participants who had read long BfArM text versions with QRD template 8 provided significantly more correct answers than with the model template when asked to locate the frequency of the side effect hair loss. This could however be due to the fact that the model template provided the information in the second column of the page rather than the first, as in QRD template 8. It has been shown in a previous study that page breaks and column changes within a chapter reduce locatability of information[53]. However in all 6 short versions of the package leaflets there was a page break within chapter 4 which did not reduce locatability of the side effect. This page break was at the same position in all leaflets and the text versions were significantly shorter and optimised. Additionally, the side effect 'hair loss' was at the start of the bullet point in all short text versions which most likely led to more correct answers through better locatability.

The model template motivated more the participants to read the leaflet in comparison to QRD template 8, led to more confidence in the medicine, and participants were more satisfied with package leaflets using this template than those with QRD template 8. A previous study has shown that increasing text volume

reduces motivation to read the leaflet and reduces confidence in the medicine[53] which supports the results shown here, as the shorter leaflets with the model template provide more motivation to read the leaflet. The results thereby show that the model template was in many aspects superior to QRD template 8, although for long BfArM text versions, the QRD template 8 increased the percentage of located information, but also increased the locatability time.

Table 79: Significant differences found in the readability test between the model template and QRD template 8

Item	Subitem	Significant advantage for		Which text versions showed significant differences			Comment	Reference
		Model template	QRD template 8	EN - short text	DE - short text	DE - long BfArM text		
Total of provided answers	Total result	x		x	x		Model template more correct answers	Table 38 Appendix 13
	Comprehens-ibility	x		x	x	x	Model template less wrong answers	Table 38 Appendix 13
	Locatability		x			x	QRD template 8 less not found answers	Appendix 13
Time	Time taken to find requested information	x				x	Using model template needed significantly less time to find requested information	Table 37
General inform-ation	Better locatability of whether the medicine available on prescription		x		x		QRD template 8 less not found answers for whether medicine is on prescription or not	Table 39 Appendix 21
Package leaflet section 2	Warnings and precautions	x		x			Model template significantly more correct answers on how to act in the case of lactose allergy	Table 44 Appendix 14
		x		x	x	x	Model template significantly less	Table 44

Item	Subitem	Significant advantage for		Which text versions showed significant differences			Comment	Reference
		Model template	QRD template 8	EN - short text	DE - short text	DE - long BfArM text		
							wrong answers on how to act in the case of lactose allergy	Appendices 17, 18, 19
			x	x	x	x	QRD template 8 significantly less not found answers on how to act in the case of lactose allergy	Table 44 Appendices 20, 21, 23
		x		x			Model template significantly more correct answers if dental operation needed	Table 46 Appendix 14
		x		x			Model template significantly less not found answers if dental operation is needed	Table 46 Appendix 20
		x				x	Model template significantly less wrong answers in the case of kidney transplant	Table 47 Appendix 19
		x		x			Model template significantly less not found answers in the case of kidney transplant in short text version	Table 47 Appendix 20

Item	Subitem	Significant advantage for		Which text versions showed significant differences			Comment	Reference
		Model template	QRD template 8	EN - short text	DE - short text	DE - long BfArM text		
			x			x	QRD template 8 significantly less not found answers in the case of kidney transplant in long BfArM text version	Table 47 Appendix 22
Package leaflet section 3	Better comprehension of method of use		x			x	QRD template 8 significantly more correct answers for whether tablet can be divided	Table 65 Appendix 16
Package leaflet section 4	Better comprehension and locatability of side effect frequencies	x		x	x	x	Model template significantly more correct answers, less wrong answers and less not found answers for 'in which of the side effect frequency groups does the following frequency: 'affects 5 in 100 people' belong?'*	Table 60 Appendices 14, 15, 16, 17, 18, 19, 20, 21, 23
	Better results of how to act in the case of side effects occurring		x	x		x	QRD template 8 significantly more correct answers on how to act if a side effect occurs	Table 61 Appendices 14, 16

Item	Subitem	Significant advantage for		Which text versions showed significant differences			Comment	Reference
		Model template	QRD template 8	EN - short text	DE - short text	DE - long BfArM text		
	Better results of how to act in the case of side effects occurring		x	x			QRD template 8 significantly less not found answers on how to act if a side effect occurs	Table 61 Appendices 20, 23
	Better comprehension and locatability of the frequency of a specific side effect		x			x	QRD template 8 more correct answers and less not found answers for ‘how frequent is the side effect ‘hair loss’?’*	Table 57 Appendices 16, 22
	Better locatability of how to act in the case of a severe side effect		x			x	QRD template 8 significantly less not found answers on which side effects require immediate contact with a doctor	Table 62 Appendix 22
Partici-pants opinion	Motivation to read the leaflet	x			**x**		Model template favoured for statement ‘the first impression of this package leaflet motivated me to	Table 69

Item	Subitem	Significant advantage for		Which text versions showed significant differences			Comment	Reference
		Model template	QRD template 8	EN - short text	DE - short text	DE - long BfArM text		
							read further'	
	Confidence in the medicine	x				x	Model template favoured for statement 'the content of this package leaflet does not raise my concerns about using this medicine'	Table 70
	Satisfaction with the package leaflet	x				x	Model template favoured for statement 'Would you like all package leaflets to be similar to this one?	Table 70
Number of significant advantages for:	Model template	-		10	7	9	Total result: The model template was superior is many aspects to QRD template 8 especially for short text versions of the package leaflets tested	-
	QRD template 8			3	2	8		

EN = English, DE = German

* If significantly more correct, less wrong answers and less not found answers were present, this result was counted three times, or if significantly more correct and less wrong answers were found, this result was counted twice

5.8 Future perspectives to improve the QRD template

Although providing no specific information regarding using a certain medicine, the analysis of package leaflets of centralised approved medicines showed that the ever expanding volume of the QRD template contributes to the volume of text increase in the package leaflet. The readability test study performed in this work has additionally shown the significant advantages of a shorter model template in comparison to both tested versions of the QRD template for a long leaflet text, with respect to less time needed to locate content (table 37), and more correct answers for short versions of the package leaflet in two languages (table 38). Keeping the QRD template concise should therefore be a priority of future versions of the template, particularly as the model template was not inferior to the current QRD template. Until use of a shorter QRD template becomes reality, MAHs should also be made aware of the fact that comprising the QRD template text by strictly applying the bracketing convention and avoiding repetitions can reduce the text volume by 20 %[55].

Use of the model template revealed that certain elements are not necessary in the QRD template and could therefore be omitted to reduce text volume. Even though the QRD template states 'user testing to date has indicated that most patients value a content listing in the package leaflet'[49], an index is not essential according to the results of this study whereby the model template was not inferior to two template versions with a contents list. Two other studies with the model template confirm these findings[52,53]. Other investigated available templates from non-EU countries also do not contain a contents list demonstrating that future versions of the template could maybe place the contents list in pointed brackets making it optional according to the type of leaflet - for a booklet, an index is useful for locating information.

Furthermore, the model template did not include an information box at the start of the leaflet. This information box provides several duplications which are found in other sections and was only a component of the template for the package leaflet in Switzerland, otherwise none of the examined countries contained an information box. The results of this study again showed that the information box is not necessary and should be deleted.

The model template strictly avoided repetitions, such as including an extra section for pregnancy and breast-feeding, and multiple repeats of the name of the active substance which reduced the length of the template text. The results comparing both QRD templates 7.3.1 and 8 to the model template illustrate that repetitions do not improve package leaflets. There were no significant differences in the number of correct answers between the model template and QRD template versions which contained a separate section for pregnancy and breast-feeding, demonstrating that repeating this information was not beneficial.

Participants using the model template provided significantly more not found answers than either QRD template when they were asked how to act if they were allergic to lactose. However, the apparent benefit of the separate subsection in the QRD templates was counteracted by the fact that the participants significantly misunderstood the wording from the Excipients Guideline[94] which means that all three template versions require improvement. One suggestion would be to integrate the Excipients Guideline warnings under the 'Warnings and precautions' heading and emphasise and/or reword the contraindication bullet point as following:

'Do not take X in the case of

- **allergy** to any ingredient of X listed in section 6'.

However, before this suggestion could be implemented, user testing is required.

Participants using the model template and QRD template 7.3.1 provided significantly more correct answers for the question 'in which of the side effect frequency groups does the following frequency: 'affects 5 in 100 people' belong?' demonstrating that this method of describing side effect frequencies was superior from both these templates compared to QRD template 8. The frequencies in QRD template 8 also led to an overestimation of frequency. These results show that a rewording of the side effect frequencies is necessary to the version recommended by the EMA[182] and BfArM[120] in 2007 for future versions of the template as it shows significantly better comprehensibility and is in line with the recommendations for the SmPC[67].

The fact that participants who had read the long BfArM text frequently provided less correct answers than the shorter text versions was often due to the wording in the BfArM text and was not dependent on the template used. This is a prerequisite which exists in general, that to be able to comprehend and locate information, that the information itself must be present and comprehensible and located under the correct heading/subheading. This was demonstrated for example by the question as to whether the tablet can be divided - this information was missing in the package leaflet version with the BfArM text; therefore both the model template and QRD template 7.3.1 provided worse results than QRD template 8 (table 65).

The question therefore arises of whether we need a shorter template if QRD template 8 is already better than 7.3.1 or comparable to the model template? For short versions of the package leaflet the model template was definitely superior in terms of the number of correct answers. For long BfArM versions of the leaflets the time needed to answer the content questions was significantly less with the model template when compared to either QRD template showing that the conciseness was important for time needed to locate the leaflet information. Additionally, the main two pieces information which were not found in the model template compared to QRD template 8 in long BfArM text versions were tablet divisibility (as

discussed above) and whether the product was available on prescription. The fact that prescription status of a product is usually a component of the outer packaging, and making inclusion of a standard text or picture regarding divisibility a necessity in the package leaflet, would however solve both these problems.

What however should be seriously considered is readability testing of new versions of the QRD template before implementation, especially in the light of findings which show that path taken by the European Commission in demanding readability testing of package leaflets themselves is suitable for improving readability.

6. Summary

Background: Package leaflets of medicines distributed within the European Union must reflect the QRD template. Since the first edition of the QRD template from 1996, thirteen revisions have followed. During development the QRD template update published in 2011, headings and mandatory texts underwent major changes based on information gained from user testing and feedback from various sources. The methods and resulting data used to create these amendments remain unpublished.

Aims of the project: This study aimed to analyse the development of the QRD template from its initial version to the present day and addressed the problem of insufficient data regarding its readability and use. Content and structure comparison of templates of non-EU countries to the QRD template was another aim.

Materials and methods: The English QRD template text intended for package leaflets of centralised approved OTC medicines was analysed regarding the number of words, and content of information contained in each section. In addition, a written readability test was carried out using package leaflets with QRD templates 7.3.1, QRD template 8 and a model template using three enalapril texts: German BfArM sample text, and a shortened German version of the BfArM sample text and its English translation. Every participant tested all three templates with a 6 month time gap in a cross-over procedure. An internet search was used to identify package leaflet templates available in English and German; the content and structure of these templates were analysed including the relevant directives and guidelines. To investigate how widely the QRD template is implemented in the practice, package leaflets for centralised approved medicines were downloaded from the EMA website three times with a year between each download.

Results: During development of the QRD template up to the present day, the number of words has increased from initially less than 100 to over 800. The continuous updating has led to wide-ranging structural and content changes in the template as well as altering the wording of many headings and standard statements. A total of 241 people from Germany and England participated in the readability test. For the short leaflet text, participants provided significantly more correct answers with the model template compared to both QRD templates. For the long BfArM sample text tested in Germany, participants provided a comparable numbers of correct answers with QRD template 8 and the model template, but significantly less when QRD template 7.3.1 had been used. Information contained in the sections for contraindications, precautions and possible side effects caused the most problems with regard to locatability and comprehensibility. Analysis of the package leaflets for centralised procedures showed that up to nearly 40 % of the text used in package leaflets can come from the QRD template.

Conclusions: The continuous updating of the QRD template can be seen as positive as improvements have been found in general headings and standard sentences. Further optimisation is however still possible by reducing the length of the text and rewording the description of side effect frequencies.

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Appendices

Appendix 1: BfArM sample text enalapril

Muster-Nr. 8000142 Stand: 07.04.2009
Dateiname: palde-enalapril-oral-2009-04-09-005

	Enalaprilmaleat	Tablette	2,5 mg / 5 mg / 10 mg / 20 mg
M2	Stoff	Darreichungsform	Stärke

PA Anlage

PB Wortlaut der für die Packungsbeilage vorgesehenen Angaben

PCX Gebrauchsinformation

Lesen Sie die gesamte Packungsbeilage / Gebrauchsinformation sorgfältig durch, bevor Sie mit der Einnahme dieses Arzneimittels beginnen.
- Heben Sie die Packungsbeilage auf. Vielleicht möchten Sie diese später nochmals lesen.
- Wenn Sie weitere Fragen haben, wenden Sie sich bitte an Ihren Arzt oder Apotheker.
- Dieses Arzneimittel wurde Ihnen persönlich verschrieben und darf nicht an Dritte weiter gegeben werden. Es kann anderen Menschen schaden, auch wenn diese dasselbe Krankheitsbild haben wie Sie.

1. Was ist /.../ und wofür wird es angewendet?
2. Was müssen Sie vor der Einnahme von /.../ beachten?
3. Wie ist /.../ einzunehmen?
4. Welche Nebenwirkungen sind möglich?
5. Wie ist /.../ aufzubewahren?
6. Weitere Angaben

[(Handels)Name Stärke Darreichungsform]

PF Wirkstoff: Enalaprilmaleat

PG Der arzneilich wirksame Bestandteil ist Enalaprilmaleat.

/Für Tabletten 2,5 mg / 5 mg / 10 mg / 20 mg:
1 Tablette enthält 2,5 mg / 5 mg / 10 mg / 20 mg Enalaprilmaleat.**/**

PH Die sonstigen Bestandteile sind:
[Angaben entsprechend der Zusammensetzung]

P4 [Darreichungsform und Inhalt / für den Patienten erhältliche Packungsgrößen]
/.../ ist in Packungen mit ... Tabletten erhältlich.

PC1 **1. WAS IST /.../ UND WOFÜR WIRD ES ANGEWENDET?**

PI 1.1 /.../ ist ein ACE-Hemmer, d.h. ein Arzneimittel mit blutdrucksenkenden und herzentlastenden Eigenschaften.

PD 1.2 von: [Name, Anschrift des pharmazeutischen Unternehmers, optional Telefon- und Telefaxnummer, E-Mail-Adresse und Internet-Adresse]

P5 hergestellt von: [Name, Anschrift des Herstellers, optional Telefon- und Telefaxnummer, E-Mail-Adresse und Internet-Adresse; kann entfallen, wenn mit pharmazeutischem Unternehmer identisch]

PK /.../ wird angewendet

- zur Behandlung eines hohen Blutdrucks (Hypertonie)
- zur Behandlung einer Herzleistungsschwäche (symptomatische Herzinsuffizienz)
- zur Vorbeugung der Entwicklung einer Herzleistungsschwäche (symptomatische Herzinsuffizienz) bei Patienten mit einer Funktionseinschränkung der linken Herzkammer, die noch keine Zeichen einer Herzleistungsschwäche verursacht (asymptomatische linksventrikuläre Dysfunktion mit einer linksventrikulären Auswurffraktion [LVEF] ≤ 35%).

PC2 **2. WAS MÜSSEN SIE VOR DER EINNAHME VON /.../ BEACHTEN?**

PL 2.1 /.../ darf nicht eingenommen werden:

- wenn sie überempfindlich (allergisch) gegenüber dem Wirkstoff Enalaprilmaleat, einen anderen ACE-Hemmer oder einen der sonstigen Bestandteile von /.../ sind
- wenn bei Ihnen während einer früheren Behandlung mit einem ACE-Hemmer Gewebeschwellungen (angioneurotische Ödeme) auftraten
- wenn Sie eine vererbte Neigung zu Gewebeschwellungen oder Gewebeschwellungen aus unbekannter Ursache haben (hereditäres oder idiopathisches Angioödem)
- während der letzten 6 Schwangerschaftsmonate. (Es wird empfohlen, [Arzneimittel] auch in der frühen Phase der Schwangerschaft nicht anzuwenden, siehe Abschnitt Schwangerschaft und Stillzeit*).'*

PV 2.2 <u>Besondere Vorsicht bei der Einnahme von /.../ ist erforderlich</u>

- Wenn Sie an folgenden Erkrankungen leiden bzw. folgende Umstände bei Ihnen vorliegen, informieren Sie bitte Ihren Arzt bevor Sie das Arzneimittel einnehmen. Dieser wird die nötigen Vorsichtsmaßnahmen treffen.
- wenn bei Ihnen das Risiko eines übermäßigen Blutdruckabfalls besteht, weil Sie an Störungen des Salz- und Flüssigkeitshaushaltes leiden, z.B. weil Sie harntreibende Arzneimittel einnehmen oder eine salzarme Diät durchführen oder als Folge von Erbrechen oder Durchfall
- wenn die Herzklappen Ihrer linken Herzkammer verengt sind oder andere Ausflussbehinderungen aus der linken Herzkammer bestehen
- wenn Sie an einer Herzerkrankung mit Unterbrechung der Durchblutung (Ischämie) leiden

- wenn Sie an Durchblutungsstörungen des Gehirns (zerebrovaskuläre Erkrankung) leiden
- wenn Ihre Nierenfunktion eingeschränkt ist (Kreatinin-Clearance unter 80 ml/Minute)
- wenn bei Ihnen eine Einengung der Nierenschlagadern vorliegt (beidseitig bzw. einseitig bei Einzelniere)
- wenn bei Ihnen kürzlich eine Nierenverpflanzung durchgeführt wurde
- wenn bei Ihnen die Leberenzymwerte ansteigen oder Sie eine Gelbsucht entwickeln
- wenn bei Ihnen die Anzahl der weißen Blutkörperchen abnimmt (Leukopenie) bzw. sich eine hochgradige Verminderung bestimmter weißer Blutkörperchen mit Infektneigung und schweren Allgemeinsymptomen (Agranulozytose) entwickelt
- wenn Sie an einer bestimmten Erkrankung des Bindegewebes (Kollagenosen) mit Gefäßbeteiligung leiden
- wenn Sie mit Arzneimitteln behandelt werden, die Ihre Abwehrreaktionen unterdrücken
- wenn Sie gleichzeitig Allopurinol (Arzneimittel gegen Gicht), Procainamid (Arzneimittel gegen Herzrhythmusstörungen) oder Lithium (Arzneimittel gegen bestimmte Depressionen) einnehmen
- wenn bei Ihnen während der Behandlung mit /.../ Überempfindlichkeitsreaktionen bzw. Gewebeschwellungen (Angio
ödeme) auftreten
- wenn Sie unter Zuckerkrankheit leiden (Diabetes mellitus)
- wenn bei Ihnen ein hartnäckiger trockner Husten auftritt
- wenn bei Ihnen das Risiko einer Erhöhung der Kaliumwerte im Blut besteht
- wenn die Blutdrucksenkung aufgrund Ihrer ethnischen Zugehörigkeit (insbesondere bei Patienten mit schwarzer Hautfarbe) nicht ausreichend stark ist.

Wenn bei Ihnen eine Desensibilisierungstherapie gegen Insektengifte (z.B. von Bienen oder Wespen) notwendig ist, ist /.../ vorübergehend durch ein geeignetes Arzneimittel aus einer anderen Stoffklasse zu ersetzen. Es können sonst lebensbedrohliche Überempfindlichkeitsreaktionen (z.B. Blutdruckabfall, Atemnot, Erbrechen, allergische Hautreaktionen) auftreten. Solche Reaktionen können auch nach Insektenstichen (von z.B. Bienen oder Wespen) vorkommen.

Die gleichzeitige Anwendung von /.../ bei einer Blutwäsche (Dialyse) mit bestimmten Dialysemembranen (High-flux-Membranen) bzw. bei einer Behandlung von stark erhöhten Blutfetten (LDL-Apherese mit Dextransulfat-Absorption) können schwere Überempfindlichkeitsreaktionen bis hin zum lebensbedrohlichen Schock auslösen.

Im Falle einer notfallmäßigen Blutwäsche oder Hämofiltration oder der Notwendigkeit einer LDL-Apherese muss deshalb vorher auf ein anderes für das betreffende Anwendungsgebiet geeignetes Arzneimittel – keinen ACE-Hemmer – umgestellt werden oder eine andere Dialysemembran verwendet werden.

Teilen Sie Ihrem Arzt mit, dass Sie mit /.../ behandelt werden bzw. Dialysen benötigen, damit der Arzt dies bei der Behandlung berücksichtigen kann.

Falls Sie vor einer Operation oder Narkose (auch beim Zahnarzt) stehen, teilen Sie Ihrem Arzt mit, dass Sie /.../ einnehmen, da es unter der Narkose zu einem plötzlichen Blutdruckabfall kommen kann.

Informieren Sie sofort Ihren Arzt, falls bei Ihnen folgende Krankheitszeichen auftreten:

- Schwellung von Gesicht, Gliedmaßen, Lippen, Schleimhaut, Zunge und/oder Kehlkopf, Atemnot
- Gelbfärbung von Haut und Schleimhäuten
- Fieber, Lymphknotenschwellung und/oder Halsentzündung.
- In diesen Fällen dürfen Sie /.../ nicht weiter einnehmen und Ihr Arzt wird entsprechende Maßnahmen ergreifen.

Die Anwendung dieses Arzneimittels bedarf der regelmäßigen ärztlichen Kontrolle. Halten Sie daher bitte die vom Arzt angeordneten Laborkontrollen und Untersuchungen unbedingt ein.

Kinder

Die Daten zur Anwendung von Enalaprilmaleat bei Kindern mit Bluthochdruck sind begrenzt. Bezüglich der anderen Anwendungsgebiete gibt es keine Daten. Zur Anwendung von Enalprilmaleat liegen Daten zur Verträglichkeit und Wirksamkeit nur zu Anwendung von Enalaprilmaleat bei Kindern ab 6 Jahren in der Behandlung von Bluthochdruck vor, daher wird /.../ für Kinder ausschließlich zur Behandlung dieser Erkrankung empfohlen.

Neugeborene und Kinder mit Nierenerkrankungen sollen nicht mit /.../ behandelt werden.

PV3 Schwangerschaft

Teilen Sie Ihrem Arzt mit, wenn Sie vermuten, schwanger zu sein oder schwanger werden könnten. In der Regel wird Ihr Arzt Ihnen empfehlen, [Arzneimittel] vor einer Schwangerschaft bzw. sobald Sie wissen, dass Sie schwanger sind, abzusetzen, und er wird Ihnen ein anderes Arzneimittel empfehlen. Die Anwendung von [Arzneimittel] in der frühen Schwangerschaft wird nicht empfohlen und [Arzneimittel] darf nicht mehr nach dem dritten Schwangerschaftsmonat eingenommen werden, da die Einnahme von [Arzneimittel] in diesem Stadium zu schweren Schädigungen Ihres ungeborenen Kindes führen kann.

PV4 Stillzeit

Teilen sie Ihrem Arzt mit, wenn Sie stillen oder mit dem Stillen beginnen wollen. Das Stillen von Neugeborenen (in den ersten Wochen nach der Geburt) und besonders von Frühgeburten wird nicht empfohlen, wenn Sie [Arzneimittel] einnehmen.
Bei älteren Säuglingen sollte der Arzt Sie über Nutzen und mögliche Schäden der Anwendung von [Arzneimittel] in der Stillzeit im Vergleich zu Behandlungsalternativen aufklären.

PV5 Verkehrstüchtigkeit und das Bedienen von Maschinen

Die Behandlung mit diesem Arzneimittel bedarf der regelmäßigen ärztlichen Kontrolle. Durch individuell auftretende unterschiedliche Reaktionen kann das Reaktionsvermögen so weit

verändert sein, dass die Fähigkeit zur aktiven Teilnahme am Straßenverkehr, zum Bedienen von Maschinen oder zum Arbeiten ohne sicheren Halt beeinträchtigt wird. Dies gilt in verstärktem Maße bei Behandlungsbeginn, Dosiserhöhung und Präparatewechsel sowie im Zusammenwirken mit Alkohol.

PN 2.3 Wechselwirkungen mit anderen Arzneimitteln

Bitte informieren Sie Ihren Arzt oder Apotheker, wenn Sie andere Arzneimittel einnehmen bzw. vor kurzem eingenommen haben, auch wenn es sich um nicht verschreibungspflichtige Arzneimittel handelt.

Bei gleichzeitiger Einnahme von /.../ und anderen Arzneimitteln ist insbesondere zu berücksichtigen:

- *Harntreibende Arzneimittel mit verminderter Kaliumausscheidung (kaliumsparende Diuretika) und Kaliumpräparate:*
  ACE-Hemmer mildern den Kaliumverlust durch harntreibende Arzneimittel. Bestimmte harntreibende Arzneimittel (kaliumsparende Diuretika, wie z. B. Spironolacton, Triamteren oder Amilorid), Kaliumpräparate, kaliumhaltige Salzersatzmittel oder Heparin (gerinnungshemmendes Arzneimittel) können zu einem deutlichen Anstieg des Kaliumwertes im Blut führen. Die gleichzeitige Anwendung sollte mit Vorsicht und unter häufiger Überprüfung der Kaliumwerte im Blut erfolgen.
- *Andere harntreibende Arzneimittel (Thiazide oder Schleifendiuretika):*
  Eine vorangegangene hoch dosierte Behandlung mit harntreibenden Arzneimitteln kann zu Volumenmangel und damit zum Risiko eines Blutdruckabfalls bei Therapiebeginn mit /.../ führen. Die blutdrucksenkende Wirkung kann durch Absetzen des harntreibenden Arzneimittels, einem Ausgleich des Volumenmangels bzw. Gabe von Salz oder durch Einleitung der Therapie mit Enalaprilmaleat in niedriger Dosierung vermindert werden.
- *Andere blutdrucksenkende Arzneimittel (Antihypertensiva):*
  Die gleichzeitige Anwendung von /.../ mit anderen blutdrucksenkenden Arzneimitteln kann die blutdrucksenkende Wirkung von /.../ verstärken. Auch die gleichzeitige Anwendung von Nitroglyzerin und anderen Nitraten oder anderen gefäßerweiternd wirkenden Arzneimitteln (Vasodilatatoren) kann den Blutdruck weiter senken.
- *Lithium (Arzneimittel gegen Depressionen):*
  Unter der gleichzeitigen Anwendung von ACE-Hemmern und Lithium wurde über reversible Anstiege der Lithiumwerte im Blut und schädliche (toxische) Effekte berichtet. Eine gleichzeitige Therapie mit bestimmten harntreibenden Arzneimitteln (Thiaziddiuretika) kann die Lithium-Konzentration im Blut und damit das Risiko einer schädlichen Wirkung von Lithium unter einer ACE-Hemmer-Therapie erhöhen. Die Anwendung von /.../ mit Lithium wird deshalb nicht empfohlen; sollte diese Kombination aber erforderlich sein, sind die Lithiumwerte im Blut sorgfältig zu überwachen.
- *Arzneimittel gegen Depressionen sowie gegen andere psychische Erkrankungen, Betäubungsmittel, Narkosemittel (trizyklische Antidepressiva, Neuroleptika, Anästhetika, Narkotika):*
  Eine gleichzeitige Anwendung mit ACE-Hemmern kann zu einer verstärkten Blutdrucksenkung führen.
- *Arzneimittel gegen Schmerzen und Entzündungen (nicht steroidale Antiphlogistika):*
  Die Dauertherapie mit Arzneimitteln gegen Schmerzen und Entzündungen kann die blutdrucksenkende Wirkung von ACE-Hemmern abschwächen. Eine gleichzeitige

Behandlung kann zu einer Erhöhung der Kaliumwerte im Blut und zu einer Verschlechterung der Nierenfunktion führen, die gewöhnlich reversibel ist. Selten kann es auch zu akutem Nierenversagen kommen, insbesondere bei Patienten mit eingeschränkter Nierenfunktion z.B. bei älteren Patienten oder Patienten mit Flüssigkeitsmangel.

- *Sympathomimetika (Mittel, die ähnliche Wirkungen wie die körpereigenen Überträgerstoffe Noradrenalin bzw. Adrenalin hervorrufen, z. B. Blutdrucksteigerung):*
  Sympathomimetika können die blutdrucksenkende Wirkung von ACE-Hemmern abschwächen.
- *Blutzuckersenkende Arzneimittel und Insulin (Antidiabetika):*
  *B*ei gleichzeitiger Anwendung mit ACE-Hemmern kann es zu einer Verstärkung der blutzuckersenkenden Wirkung kommen; es besteht das Risiko, dass Blutzuckerwerte unter Normalwerte absinken (Hypoglykämie). Diese Fälle treten offenbar insbesondere in den ersten Wochen der kombinierten Behandlung sowie bei Patienten mit eingeschränkter Nierenfunktion auf.
- *Acetylsalicylsäure (Arzneimittel, das in niedriger Dosierung zum Schutz vor Herz-Kreislauf-Erkrankungen eingesetzt wird), Arzneimittel zur Auflösung von Blutgerinnseln (Thrombolytika), Betablocker (Arzneimittel z.B. zur Behandlung des Bluthochdrucks):*
  Eine gleichzeitige Behandlung mit /.../ kann erfolgen.

2.4 Bei Einnahme von /.../ zusammen mit Nahrungsmitteln und Getränken:

Die Nahrungsaufnahme hat keinen Einfluss auf die Aufnahme von /.../ in den Körper.

Alkohol verstärkt die blutdrucksenkende Wirkung von ACE-Hemmern.

PC3 **3. Wie ist /.../ einzunehmen?**

PMX Nehmen Sie /.../ immer genau nach der Anweisung des Arztes ein. Bitte fragen Sie bei Ihrem Arzt oder Apotheker nach, wenn Sie sich nicht ganz sicher sind.
Es ist sehr wichtig, dass Sie /.../ einnehmen, solange es Ihnen Ihr Arzt verordnet.

3.1 Art der Anwendung

Tabletten zum Einnehmen.

3.2 Ihr Arzt wird Ihre anfängliche Dosis individuell nach Ihrem Gesundheitszustand und dem Schweregrad Ihrer Erkrankung wählen und entsprechend der Wirkung des Arzneimittels auf Ihren Blutdruck die Dosis schrittweise anpassen.

Falls vom Arzt nicht anders verordnet, ist die übliche

Dosis:

/Für Tabletten 2,5 mg:

Bluthochdruck

Anfangsdosis:

Die Anfangsdosis beträgt 1-mal täglich 2 Tabletten /.../ (entsprechend 5 mg Enalaprilmaleat) bis maximal 20 mg
Enalaprilmaleat je nach Schweregrad der Erkrankung und Ihrem Zustand.

- Leichter Bluthochdruck:
  Die empfohlene Anfangsdosis beträgt 1-mal täglich 2 Tabletten /.../ (entsprechend 5 mg Enalaprilmaleat) bis zu 10 mg Enalaprilmaleat täglich.

- Patienten mit stark aktiviertem blutdruckregulierendem System z. B. bei Bluthochdruck aufgrund einer Nierenerkrankung, Salz- und/oder Flüssigkeitsmangel, nicht ausgeglichener Herzleistungsschwäche oder schwerem Bluthochdruck:
  Die Therapie wird mit 1-mal täglich 2 Tabletten /.../ (entsprechend 5 mg Enalaprilmaleat) oder einer geringeren Dosis eingeleitet. Bei Therapiebeginn kann es zu einem übermäßigen Blutdruckabfall kommen; eine engmaschige ärztliche Überwachung ist erforderlich.

- Patienten mit vorausgegangener Therapie mit hoch dosierten harn-treibenden Arzneimitteln (Diuretika):
  Die Therapie wird mit 1-mal täglich 2 Tabletten /.../ (entsprechend 5 mg Enalaprilmaleat) oder einer geringeren Dosis eingeleitet.
  Eine vorausgegangene Therapie mit hoch dosierten harntreibenden Arzneimitteln kann zu einem Flüssigkeitsmangel führen, so dass die Gefahr eines Blutdruckabfalls bei Therapiebeginn besteht. Wenn möglich sollten diese Arzneimittel 2-3 Tage lang abgesetzt werden, bevor die Therapie mit /.../ eingeleitet wird. Die Nierenfunktion und die Kaliumwerte im Blut sollten überwacht werden.

Erhaltungsdosis:

Die übliche Erhaltungsdosis beträgt 20 mg Enalaprilmaleat täglich. Eine Tageshöchstdosis von 40 mg Enalaprilmaleat sollte nicht überschritten werden.

Für die höheren Dosierungen stehen Tabletten mit geeigneter Wirkstoffstärke zur Verfügung.

Herzleistungsschwäche (symptomatische Herzinsuffizienz)/ Funktionsstörung der linken Herzkammer (asymptomatische linksventrikuläre Dysfunktion)

Anfangsdosis:

/.../ wird bei der Behandlung der Herzleistungsschwäche üblicherweise zusätzlich zu harntreibenden Arzneimitteln und Digitalis oder Betablockern angewendet.

Die Anfangsdosis beträgt 1-mal täglich 1 Tablette /.../ (entsprechend 2,5 mg Enalaprilmaleat).

Die Therapie ist unter engmaschiger ärztlicher Überwachung einzuleiten, um die anfängliche Wirkung auf den Blutdruck zu ermitteln.

Erhaltungsdosis:

Zu Beginn der Therapie mit /.../ kann es bei Patienten mit Herzleistungsschwäche zu einem Blutdruckabfall kommen. Wenn dieser behoben ist, sollte die Dosis schrittweise über einen Zeitraum von 2-4 Wochen auf die Erhaltungsdosis von 20 mg Enalaprilmaleat täglich gesteigert werden. Diese Dosis kann als Ein zeldosis eingenommen oder auf zwei Gaben verteilt werden, je nach Verträglichkeit.

Eine Tageshöchstdosis von 40 mg Enalaprilmaleat, auf
2 Gaben verteilt, sollte nicht überschritten werden.

Für die höheren Dosierungen stehen Tabletten mit geeigneter Wirkstoffstärke zur Verfügung.***/***

/Für Tabletten 5 mg:

Bluthochdruck

Anfangsdosis:

Die Anfangsdosis beträgt 1-mal täglich 1 Tablette /.../ (entsprechend 5 mg Enalaprilmaleat) bis maximal 20 mg Enalaprilmaleat je nach Schweregrad der Erkrankung und Ihrem Zustand.

- Leichter Bluthochdruck:
  Die empfohlene Anfangsdosis beträgt 1-mal täglich 1 Tablette /.../ (entsprechend 5 mg Enalaprilmaleat) bis 1-mal täglich 2 Tabletten /.../ (entsprechend 10 mg Enalaprilmaleat).
- Patienten mit stark aktiviertem blutdruckregulierendem System z. B. bei Bluthochdruck aufgrund einer Nierenerkrankung, Salz- und/oder Flüssigkeitsmangel, nicht ausgeglichener Herzleistungsschwäche oder schwerem Bluthochdruck:
  Die Therapie wird mit 1-mal täglich 1 Tablette /.../ (entsprechend 5 mg Enalaprilmaleat) oder einer geringeren Dosis eingeleitet. Bei Therapiebeginn kann es zu einem übermäßigen Blutdruckabfall kommen; eine engmaschige ärztliche Überwachung ist erforderlich.
- Patienten mit vorausgegangener Therapie mit hoch dosierten harntreibenden Arzneimitteln (Diuretika):
  Die Therapie wird mit 1-mal täglich 1 Tablette /.../ (entsprechend 5 mg Enalaprilmaleat) oder einer geringeren Dosis eingeleitet.

Eine vorausgegangene Therapie mit hoch dosierten harntreibenden Arzneimitteln kann zu einem Flüssigkeitsmangel führen, so dass die Gefahr eines Blutdruckabfalls bei Therapiebeginn besteht. Wenn möglich sollten diese Arzneimittel 2-3 Tage lang abgesetzt werden, bevor die Therapie mit /.../ eingeleitet wird. Die Nierenfunktion und die Kaliumwerte im Blut sollten überwacht werden.

Erhaltungsdosis:

Die übliche Erhaltungsdosis beträgt 20 mg Enalaprilmaleat täglich. Eine Tageshöchstdosis von 40 mg Enalaprilmaleat sollte nicht überschritten werden.

Für die höheren Dosierungen stehen Tabletten mit geeigneter Wirkstoffstärke zur Verfügung.

Herzleistungsschwäche (symptomatische Herzinsuffizienz)/ Funktionsstörung der linken Herzkammer (asymptomatische linksventrikuläre Dysfunktion)

Anfangsdosis:

/.../ wird bei der Behandlung der Herzleistungsschwäche üblicherweise zusätzlich zu harntreibenden Arzneimitteln und Digitalis oder Betablockern angewendet.

Die Anfangsdosis beträgt 1-mal täglich 2,5 mg Enalaprilmaleat.

Die Therapie ist unter engmaschiger ärztlicher Überwachung einzuleiten, um die anfängliche Wirkung auf den Blutdruck zu ermitteln.

Erhaltungsdosis:

Zu Beginn der Therapie mit /.../ kann es bei Patienten mit Herzleistungsschwäche zu einem Blutdruckabfall kommen. Wenn dieser behoben ist, sollte die Dosis schrittweise über einen

Zeitraum von 2-4 Wochen auf die Erhaltungsdosis von 20 mg Enalaprilmaleat täglich gesteigert werden. Diese Dosis kann als Einzeldosis eingenommen oder auf zwei Gaben verteilt werden, je nach Verträglichkeit.

Eine Tageshöchstdosis von 40 mg Enalaprilmaleat, auf 2 Gaben verteilt, sollte nicht überschritten werden.

Für die höheren Dosierungen stehen Tabletten mit geeigneter Wirkstoffstärke zur Verfügung.**/**

/Für Tabletten 10 mg:

Bluthochdruck

Anfangsdosis:

Die Anfangsdosis beträgt 1-mal täglich 5 mg Enalaprilmaleat bis maximal 20 mg Enalaprilmaleat je nach Schweregrad der Erkrankung und Ihrem Zustand.

- Leichter Bluthochdruck:
  Die empfohlene Anfangsdosis beträgt 1-mal täglich 5 mg Enalaprilmaleat bis zu 1-mal täglich 1 Tablette /.../ (entsprechend 10 mg Enalaprilmaleat) täglich.
- Patienten mit stark aktiviertem blutdruckregulierendem System z. B. bei Bluthochdruck aufgrund einer Nierenerkrankung, Salz- und/oder Flüssigkeitsmangel, nicht ausgeglichener Herzleistungsschwäche oder schwerem Bluthochdruck:
  Die Therapie wird mit 1-mal täglich 5 mg Enalaprilmaleat oder einer geringeren Dosis eingeleitet. Bei Therapiebeginn kann es zu einem übermäßigen Blutdruckabfall kommen; eine engmaschige ärztliche Überwachung ist erforderlich.
- Patienten mit vorausgegangener Therapie mit hoch dosierten harn-treibenden Arzneimitteln (Diuretika):
  Die Therapie wird mit 1-mal täglich 5 mg Enalaprilmaleat oder einer geringeren Dosis eingeleitet. Eine vorausgegangene Therapie mit hoch dosierten harntreibenden Arzneimitteln kann zu einem Flüssigkeitsmangel führen, so dass die Gefahr eines Blutdruckabfalls bei Therapiebeginn besteht. Wenn möglich sollten diese Arzneimittel 2-3 Tage lang abgesetzt werden, bevor die Therapie mit /.../ eingeleitet wird. Die Nierenfunktion und die Kaliumwerte im Blut sollten überwacht werden.

Erhaltungsdosis:

Die übliche Erhaltungsdosis beträgt 2 Tabletten /.../ (entsprechend 20 mg Enalaprilmaleat) täglich. Eine Tageshöchstdosis von 40 mg Enalaprilmaleat sollte nicht überschritten werden.

Für die niedrigeren und höheren Dosierungen stehen Tabletten mit geeigneter Wirkstoffstärke zur Verfügung.

Herzleistungsschwäche (symptomatische Herzinsuffizienz)/ Funktionsstörung der linken Herzkammer (asymptomatische linksventrikuläre Dysfunktion)

Anfangsdosis:

/.../ wird bei der Behandlung der Herzleistungsschwäche üblicherweise zusätzlich zu harntreibenden Arzneimitteln und Digitalis oder Betablockern angewendet.

Die Anfangsdosis beträgt 1-mal täglich 2,5 mg Enalaprilmaleat.

Die Therapie ist unter engmaschiger ärztlicher Überwachung einzuleiten, um die anfängliche Wirkung auf den Blutdruck zu ermitteln.

Erhaltungsdosis:

Zu Beginn der Therapie mit /.../ kann es bei Patienten mit Herzleistungsschwäche zu einem Blutdruckabfall kommen. Wenn dieser behoben ist, sollte die Dosis schrittweise über einen Zeitraum von 2-4 Wochen auf die Erhaltungsdosis von 2 Tabletten /.../ (entsprechend 20 mg Enalaprilmaleat) täglich gesteigert werden. Diese Dosis kann als Einzeldosis eingenommen oder auf zwei Gaben verteilt werden, je nach Verträglichkeit.

Eine Tageshöchstdosis von 40 mg Enalaprilmaleat, auf 2 Gaben verteilt, sollte nicht überschritten werden.

Für die niedrigeren und höheren Dosierungen stehen Tabletten mit geeigneter Wirkstoffstärke zur Verfügung.***/***

/Für Tabletten 20 mg:

Bluthochdruck

Anfangsdosis:

Die Anfangsdosis beträgt 1-mal täglich 5 mg Enalaprilmaleat bis maximal 1-mal täglich 1 Tablette /.../ (entsprechend 20 mg Enalaprilmaleat) je nach Schweregrad der Erkrankung und Ihrem Zustand.

- Leichter Bluthochdruck:
  Die empfohlene Anfangsdosis beträgt 1-mal täglich 5 mg Enalaprilmaleat bis zu 10 mg Enalaprilmaleat täglich.
- Patienten mit stark aktiviertem blutdruckregulierendem System z. B. bei Bluthochdruck aufgrund einer Nierenerkrankung, Salz- und/oder Flüssigkeitsmangel, nicht ausgeglichener Herzleistungsschwäche oder schwerem Bluthochdruck:
  Die Therapie wird mit 1-mal täglich 5 mg Enalaprilmaleat oder einer geringeren Dosis eingeleitet. Bei Therapiebeginn kann es zu einem übermäßigen Blutdruckabfall kommen; eine engmaschige ärztliche Überwachung ist erforderlich.
- Patienten mit vorausgegangener Therapie mit hoch dosierten harn-treibenden Arzneimitteln (Diuretika):
  Die Therapie wird mit 1-mal täglich 5 mg Enalaprilmaleat oder einer geringeren Dosis eingeleitet.
  Eine vorausgegangene Therapie mit hoch dosierten harntreibenden Arzneimitteln kann zu einem Flüssigkeitsmangel führen, so dass die Gefahr eines Blutdruckabfalls bei Therapiebeginn besteht. Wenn möglich sollten diese Arzneimittel 2-3 Tage lang abgesetzt werden, bevor die Therapie mit /.../ eingeleitet wird. Die Nierenfunktion und die Kaliumwerte im Blut sollten überwacht werden.

Erhaltungsdosis:

Die übliche Erhaltungsdosis beträgt 1-mal täglich 1 Tablette /.../ (entsprechend 20 mg Enalaprilmaleat). Eine Tageshöchstdosis von 40 mg Enalaprilmaleat sollte nicht überschritten werden.

Für die niedrigeren Dosierungen stehen Tabletten mit geeigneter Wirkstoffstärke zur Verfügung.

Herzleistungsschwäche (symptomatische Herzinsuffizienz)/ Funktionsstörung der linken Herzkammer (asymptomatische linksventrikuläre Dysfunktion)

Anfangsdosis:

/.../ wird bei der Behandlung der Herzleistungsschwäche üblicherweise zusätzlich zu harntreibenden Arzneimitteln und Digitalis oder Betablockern angewendet.

Die Anfangsdosis beträgt 1-mal täglich 2,5 mg Enalaprilmaleat.

Die Therapie ist unter engmaschiger ärztlicher Überwachung einzuleiten, um die anfängliche Wirkung auf den Blutdruck zu ermitteln.

Erhaltungsdosis:

Zu Beginn der Therapie mit /.../ kann es bei Patienten mit Herzleistungsschwäche zu einem Blutdruckabfall kommen. Wenn dieser behoben ist, sollte die Dosis schrittweise über einen Zeitraum von 2-4 Wochen auf die Erhaltungsdosis von 20 mg Enalaprilmaleat täglich gesteigert werden. Diese Dosis kann als Einzeldosis eingenommen oder auf zwei Gaben verteilt werden, je nach Verträglichkeit.

Eine Tageshöchstdosis von 2-mal 1 Tablette /.../ (entsprechend 40 mg Enalaprilmaleat), auf 2 Gaben verteilt, sollte nicht überschritten werden.

Für die niedrigeren Dosierungen stehen Tabletten mit geeigneter Wirkstoffstärke zur Verfügung.***//***

Sie sollten besonders vorsichtig sein, wenn Sie Ihre erste Dosis einnehmen oder wenn Ihre Dosis erhöht wird. Teilen Sie Ihrem Arzt unverzüglich mit, wenn Sie sich benommen oder schwindlig fühlen.

Vor und nach Beginn der Einnahme von /.../ sollten Blutdruck und Nierenfunktion engmaschig überwacht werden, da über Blutdruckabfall und (seltener) nachfolgendem Nierenversagen berichtet wurde. Wenn Sie mit harntreibenden Arzneimitteln behandelt werden, sollte – falls möglich – deren Dosis vor Beginn der Einnahme von /.../ verringert werden. Ein Blutdruckabfall bei Therapiebeginn mit /.../ bedeutet nicht, dass auch während der Dauerbehandlung mit /.../ solche Reaktionen auftreten werden und schließt die Weiterbehandlung mit dem Arzneimittel nicht aus. Die Kaliumwerte im Blut und die Nierenfunktion sollten ebenfalls überwacht werden.

Dosierung bei eingeschränkter Nierenfunktion

Grundsätzlich sollten die Abstände zwischen den Anwendungen von /.../ verlängert werden und/oder die Dosis reduziert werden.

Ihr Arzt wird Ihre Behandlung individuell festlegen.

Bei mäßiger Einschränkung der Nierenfunktion wird eine Dosis von 1-mal täglich 5-10 mg Enalaprilmaleat empfohlen.

Bei schwerer Nierenfunktionseinschränkung wird eine Dosis von 1-mal täglich 2,5 mg Enalaprilmaleat empfohlen.

Für Dialysepatienten wird eine Dosis von 1-mal täglich 2,5 mg Enalaprilmaleat an Dialyse-Tagen empfohlen. An dialysefreien Tagen richtet sich die Dosis nach der Blutdrucksenkung.

Dosierung bei älteren Patienten

Die Dosis sollte sich nach der Nierenfunktion des Patienten richten.

Dosierung bei Kindern

Wenn die Kinder Tabletten schlucken können, wird die Dosis vom Arzt individuell dem Zustand des Kindes und der Blutdrucksenkung angepasst.

Die empfohlene Anfangsdosis für Kinder mit Bluthochdruck und mit einem Gewicht von 20 kg bis 50 kg beträgt 1-mal täglich 2,5 mg Enalaprilmaleat; Kinder, die mehr als 50 kg wiegen, erhalten 1-mal täglich 5 mg Enalaprilmaleat. Die weitere Dosierung wird vom Arzt dem Bedarf des Kindes angepasst. Dabei darf eine Tageshöchstdosis von 20 mg Enalaprilmaleat für Kinder mit 20 kg bis 50 kg Körpergewicht bzw. 40 mg Enalaprilmaleat für Kinder mit mehr als 50 kg Körpergewicht nicht überschritten werden.

Neugeborene und Kinder mit Nierenerkrankungen sollen nicht mit /.../ behandelt werden.

Nehmen Sie die Tabletten unzerkaut mit ausreichend Flüssigkeit (z.B. einem Glas Wasser) ein. Die Einnahme kann unabhängig von den Mahlzeiten erfolgen. Die angegebene Tagesmenge wird in der Regel morgens auf einmal eingenommen, kann aber gegebenenfalls auch auf 2 Einnahmen morgens und abends verteilt werden.

Die Dauer der Behandlung bestimmt Ihr Arzt. Die Behandlung mit /.../ ist in der Regel eine Langzeittherapie.

Bitte sprechen Sie mit Ihrem Arzt, wenn Sie den Eindruck haben, dass die Wirkung von /...zu stark oder zu schwach ist.

3.3 Wenn Sie eine größere Menge /.../ eingenommen haben, als Sie sollten:

Wenn Sie durch ein Versehen zu viele Tabletten eingenommen haben oder ein Kind einige Tabletten geschluckt hat, wenden Sie sich sofort an einen Arzt/Notarzt. Dieser kann entsprechend der Schwere der Vergiftung über die erforderlichen Maßnahmen entscheiden.

In Abhängigkeit vom Ausmaß der Überdosierung sind folgende Symptome möglich:
Starker Blutdruckabfall, starker Blutdruckabfall, Kreislaufversagen, beschleunigter oder verlangsamter Herzschlag, Herzklopfen, Nierenversagen, Atembeschleunigung, Schwindel, Angstgefühl und Husten. Bei Verdacht auf eine Überdosierung benötigen Sie ärztliche Hilfe!

3.4 Wenn Sie die Einnahme von /.../ vergessen haben:

Nehmen Sie beim nächsten Mal nicht zusätzlich mehr Tabletten ein, sondern setzen Sie die Einnahme von /.../ wie verordnet fort.

3.5 Auswirkungen, wenn die Behandlung mit /.../ abgebrochen wird:

Unterbrechen oder beenden Sie die Behandlung mit /.../ nicht ohne Rücksprache mit Ihrem behandelnden Arzt!

Bei Patienten mit Bluthochdruck kann der Blutdruck erneut ansteigen und bei Patienten mit Herzleistungsschwäche können die Symptome wieder auftreten.

PC4 **4. WELCHE NEBENWIRKUNGEN SIND MÖGLICH?**

PM Wie alle Arzneimittel kann /.../ Nebenwirkungen haben. Diese treten jedoch nicht bei jedem Patienten auf. Unerwünschte Wirkungen, die von /.../ oder anderen ACE-Hemmern bekannt sind, finden Sie nachfolgend.

Bei der Bewertung von Nebenwirkungen werden folgende Häufigkeitsangaben zugrunde gelegt:

Sehr häufig:	mehr als 1 von 10 Behandelten
Häufig:	weniger als 1 von 10, aber mehr als 1 von 100 Behandelten
Gelegentlich:	weniger als 1 von 100, aber mehr als 1 von 1000 Behandelten
Selten:	weniger als 1 von 1.000, aber mehr als 1 von 10.000 Behandelten
Sehr selten:	weniger als 1 von 10.000 Behandelten, einschließlich Einzelfälle

4.1 Nebenwirkungen

Blut- und Lymphsystem

Gelegentlich: Blutarmut durch vermehrten Zerfall roter Blutkörperchen(hämölytische Anämie), Blutarmut durch Blutbildungsstörung im Knochenmark (aplastische Anämie).

Selten: Verminderung der Anzahl bestimmter Blutzellen (Neutropenie, Thrombozytopenie, Panzytopenie) bis zu einer hochgradigen Verminderung bestimmter weißer Blutkörperchen mit Infektneigung und schweren Allgemeinsymptomen (Agranulozytose), Abnahme bestimmter Laborwerte (Hämoglobin und Hämatokrit), herabgesetzte Funktion des Knochenmarks (Knochenmarksdepression), Lymphknotenschwellung, Autoimmunkrankheiten.

Stoffwechsel

Gelegentlich: Zu niedrige Blutzuckerwerte (Hypoglykämie).

Augen

Sehr häufig: Verschwommensehen.

Nervensystem

Häufig: Kopfschmerzen, Depressionen.

Gelegentlich: Verwirrtheitszustände, Schläfrigkeit, Schlaflosigkeit, Nervosität, Missempfindungen (z.B. Kribbeln, pelziges Gefühl), Schwindel (Vertigo).
Selten: Verändertes Träumen, Schlafstörungen.

Herz-Kreislauf-System

Sehr häufig: Schwindel.
Häufig: Übermäßige Blutdrucksenkung einschließlich übermäßiger Blutdruckabfall bei Lagewechsel vom Liegen zum Stehen (orthostatische Hypotonie), kurzzeitiger Bewusstseinsverlust (Synkope), Herzinfarkt oder Schlaganfall, vermutlich infolge übermäßigen Blutruckabfalls bei gefährdeten Patienten (Patienten mit Durchblutungsstörungen im Bereich des Herzens und/oder des Gehirns), Schmerzen im Brustkorb, Herzrhythmusstörungen, Herzengegefühl (Angina pectoris), beschleunigter Herzschlag (Tachykardie).
Gelegentlich: Übermäßiger Blutdruckabfall bei Lagewechsel vom Liegen zum Stehen (orthostatische Hypotonie), Herzklopfen.
Selten: Durch Gefäßkrämpfe bedingte Durchblutungsstörungen an Händen und Füßen (Raynaud-Phänomen).

Atemwege

Sehr häufig: Husten.
Häufig: Atemnot (Dyspnoe).
Gelegentlich: Verstärkte Schleimabsonderung aus der Nase (Rhinorrhö), Halsschmerzen und Heiserkeit, krampfartige Verengung der Bronchien (Bronchospasmus), Asthma.
Selten: Auffälligkeiten im Lungengewebe (pulmonale Infiltrate), Schnupfen, allergische Entzündungen der Lunge (allergische Alveolitis /eosinophile Pneumonie).

Magen-Darm-Trakt

Sehr häufig: Übelkeit.
Häufig: Durchfall, Bauchschmerzen, Geschmacksveränderungen.
Gelegentlich: Darmverschluss (Ileus), Entzündung der Bauchspeicheldrüse, Erbrechen, Verdauungsstörungen, Verstopfung, Appetitlosigkeit, Magenreizung, Mundtrockenheit, Magengeschwür (peptisches Ulkus).
Selten: Entzündungen der Mundschleimhaut mit Geschwürbildung (Stomatitis/aphthöse Ulzerationen), Entzündungen der Zungenschleimhaut (Glossitis).
Sehr selten: Gewebeschwellung des Darms (intestinales angioneurotisches Ödem).

Leber und Galle

Selten: Leberversagen, Leberentzündung (Hepatitis - hepatozellulär oder cholestatisch, einschließlich hepatische Nekrose), Gelbsucht.

Haut und Unterhautgewebe

Häufig: Ausschlag, Überempfindlichkeit/Gewebeschwellung (angioneurotisches Ödem): angioneurotische Ödeme mit Beteiligung von Gesicht, Gliedmaßen, Lippen, Zunge, Stimmapparat des Kehlkopfes (Glottis) und/oder Kehlkopf wurden beobachtet.
Gelegentlich: Vermehrtes Schwitzen, Juckreiz, Nesselsucht, Haarausfall.
Selten: Schwerwiegende Hautreaktionen (Erythema multiforme, Stevens-Johnson-Syndrom, exfoliative Dermatitis, toxische epidermale Nekrolyse, Pemphigus, Erythroderma).

Ein Symptomenkomplex wurde beschrieben, der mit einigen oder allen der folgenden Nebenwirkungen einhergehen kann: Fieber, Entzündung seröser Häute (Serositis), Gefäßentzündung (Vaskulitis), Muskel- und Gelenkschmerzen/Muskel- und Gelenkentzündungen (Myalgien/Myositis, Arthralgien/ Arthritis) und bestimmten Laborwertveränderungen (positive ANA-Titer, erhöhte Blutkörperchensenkungsgeschwindigkeit , Eosinophilie und Leukozytose). Hautausschlag, Lichtempfindlichkeit oder andere Reaktionen der Haut können auftreten.

Nieren und ableitende Harnwege

Gelegentlich: Nierenfunktionsstörungen, Nierenversagen, vermehrte Eiweißausscheidung im Urin (Proteinurie).
Selten: Verminderte Harnausscheidung (Oligurie).

Fortpflanzungsorgane und Brust

Gelegentlich: Impotenz.
Selten: Vergrößerung der Brust bei Männern (Gynäkomastie).

Allgemein

Sehr häufig: Schwächegefühl.
Häufig: Müdigkeit.
Gelegentlich: Muskelkrämpfe, Gesichtsrötung (Flush), Ohrgeräusche (Tinnitus), Unwohlsein, Fieber.

Laborwerte

Häufig: Anstieg der Kaliumwerte im Blut, Anstieg der Kreatininwerte im Blut.
Gelegentlich: Anstieg des Harnstoffs im Blut, Abnahme der Natriumwerte im Blut.
Selten: Erhöhte Leberwerte (Leberenzyme, Serum-Bilirubin).

4.2. Gegenmaßnahmen

Falls Sie den Verdacht haben, dass sich bei Ihnen eine schwerwiegende Hautreaktion entwickelt, müssen Sie sofort Ihren Arzt aufsuchen und gegebenenfalls die Behandlung mit /.../ abgebrechen.

Eine Gewebeschwellung (angioneurotisches Ödem) mit Beteiligung von Kehlkopf, Stimmapparat des Kehlkopfes und/oder Zunge muss von Ihrem Arzt sofort mit Notfallmedikamenten behandelt werden.

Wenn bei Ihnen eine Gelbsucht auftritt oder die Leberenzymwerte bei Ihnen deutlich ansteigen, müssen Sie die Behandlung abbrechen, und Ihr Arzt wird Sie überwachen.

Beim Auftreten von Fieber, Lymphknotenschwellungen und/oder Halsentzündung benachrichtigen Sie bitte umgehend Ihren Arzt, damit er das weiße Blutbild untersuchen kann.

Sollten Sie die oben genannten Nebenwirkungen bei sich beobachten, benachrichtigen Sie Ihren Arzt. Er wird über den Schweregrad und gegebenenfalls über erforderliche weitere Maßnahmen entscheiden.

4.3 Informieren Sie Ihren Arzt oder Apotheker, wenn Sie Nebenwirkungen bermerken, die nicht in dieser Packungsbeilage aufgeführt sind.

PC5 **5. WIE IST /.../ AUFZUBEWAHREN?**

Arzneimittel für Kinder unzugänglich aufbewahren.

PZ Sie dürfen das Arzneimittel nach dem auf dem [Packmittel] angegebenen Verfallsdatum nicht mehr verwenden.

P1 <Hinweis auf Haltbarkeit nach Anbruch oder Zubereitung>

P2 Tabletten vor Licht schützen!

P9 <Sie dürfen /.../ nicht verwenden, wenn Sie folgendes bemerken: {Beschreibung der sichtbaren Anzeichen von Nichtverwendbarkeit}>

P6 Stand der Information:

PC6 **6. WEITERE ANGABEN**

Appendix 2: German BfArM text package leaflet with model template

Lesen Sie bitte aufmerksam die Packungsbeilage!

Enal 20 mg Tabletten

1. Wofür wird Enal verwendet?

Enal wird angewendet:
- zur Behandlung eines hohen Blutdrucks (Hypertonie)
- zur Behandlung einer Herzleistungsschwäche (symptomatische Herzinsuffizienz)
- zur Vorbeugung der Entwicklung einer Herzleistungsschwäche (symptomatische Herzinsuffizienz) bei Patienten mit einer Funktionseinschränkung der linken Herzkammer, die noch keine Zeichen einer Herzleistungsschwäche verursacht (asymptomatische linksventrikuläre Dysfunktion mit einer linksventrikulären Auswurffraktion [LVEF] ≤ 35%).

Enal ist ein ACE-Hemmer, d. h. ein Arzneimittel mit blutdrucksenkenden und herzentlastenden Eigenschaften.

2. Was müssen Sie vor Einnahme von Enal beachten?

Nicht einnehmen bei/in
- Allergie gegen Enalapril, einen anderen ACE-Hemmer oder einen der in Abschnitt 6. genannten sonstigen Bestandteile dieses Arzneimittels
- Gewebeschwellungen (angioneurotische Ödeme) während einer früheren Behandlung mit einem ACE-Hemmer
- vererbter Neigung zu Gewebeschwellungen oder Gewebeschwellungen aus unbekannter Ursache (hereditäres oder idiopathisches Angioödem)
- den letzten 6 Monaten der Schwangerschaft (Es wird empfohlen, Enal auch in der frühen Phase der Schwangerschaft nicht anzuwenden, siehe Abschnitt „Erst nach Arztrücksprache einnehmen bei").

Erst nach Arztrücksprache einnehmen bei
- Risiko eines übermäßigen Blutdruckabfalls, weil Sie an Störungen des Salz- und Flüssigkeitshaushaltes leiden, z.B. weil Sie harntreibende Arzneimittel einnehmen oder eine salzarme Diät durchführen oder als Folge von Erbrechen oder Durchfall
- verengten Herzklappen Ihrer linken Herzkammer oder anderen Ausflussbehinderungen aus der linken Herzkammer
- Herzerkrankung mit Unterbrechung der Durchblutung (Ischämie)
- Durchblutungsstörungen des Gehirns (zerebrovaskuläre Erkrankung)
- eingeschränkter Nierenfunktion (Kreatinin-Clearance unter 80 ml/Minute)
- Einengung der Nierenschlagadern (beidseitig bzw. einseitig bei Einzelniere)
- kürzlich durchgeführter Nierenverpflanzung
- Anstieg der Leberenzymwerte oder Gelbsucht
- Abnahme der Anzahl weißer Blutkörperchen (Leukopenie) bzw. hochgradiger Verminderung bestimmter weißer Blutkörperchen mit Infektneigung und schweren Allgemeinsymptomen (Agranulozytose)
- einer bestimmten Erkrankung des Bindegewebes (Kollagenosen) mit Gefäßbeteiligung
- Behandlung mit Arzneimitteln, die Ihre Abwehrreaktionen unterdrücken
- gleichzeitiger Einnahme von Allopurinol (Arzneimittel gegen Gicht), Procainamid (Arzneimittel gegen Herzrhythmusstörungen) oder Lithium (Arzneimittel gegen bestimmte Depressionen) einnehmen
- Auftreten während der Behandlung mit Enal von Überempfindlichkeitsreaktionen bzw. Gewebeschwellungen (Angioödeme)
- Zuckerkrankheit (Diabetes mellitus)
- hartnäckigen, trocknen Husten
- Risiko einer Erhöhung der Kaliumwerte im Blut
- unzureichender Blutdrucksenkung aufgrund Ihrer ethnischen Zugehörigkeit (insbesondere bei Patienten mit schwarzer Hautfarbe)
- Schwangerschaft
  Teilen Sie Ihrem Arzt mit, wenn Sie vermuten, schwanger zu sein oder schwanger werden könnten. In der Regel wird Ihr Arzt Ihnen empfehlen, Enal vor einer Schwangerschaft bzw. sobald Sie wissen, dass Sie schwanger sind, abzusetzen, und er wird Ihnen ein anderes Arzneimittel empfehlen. Die Anwendung von Enal in der frühen Schwangerschaft wird nicht empfohlen und Enal darf nicht mehr nach dem dritten Schwangerschaftsmonat eingenommen werden, da die Einnahme von Enal in diesem Stadium zu schweren Schädigungen Ihres ungeborenen Kindes führen kann.
- Stillzeit
  Teilen sie Ihrem Arzt mit, wenn Sie stillen oder mit dem Stillen beginnen wollen. Das Stillen von Neugeborenen (in den ersten Wochen nach der Geburt) und besonders von Frühgeburten wird nicht empfohlen, wenn Sie Enal einnehmen.
  Bei älteren Säuglingen sollte der Arzt Sie über Nutzen und mögliche Schäden der Anwendung von Enal in der Stillzeit im Vergleich zu Behandlungsalternativen aufklären.

Wenn bei Ihnen eine Desensibilisierungstherapie gegen Insektengifte (z.B. von Bienen oder Wespen) notwendig ist, ist Enal vorübergehend durch ein geeignetes Arzneimittel aus einer anderen Stoffklasse zu ersetzen. Es können sonst lebensbedrohliche Überempfindlichkeitsreaktionen (z.B. Blutdruckabfall, Atemnot, Erbrechen, allergische Hautreaktionen) auftreten. Solche Reaktionen können auch nach Insektenstichen (von z.B. Bienen oder Wespen) vorkommen.

Die gleichzeitige Anwendung von Enal bei einer Blutwäsche (Dialyse) mit bestimmten Dialysemembranen (High-flux-Membranen) bzw. bei einer Behandlung von stark erhöhten Blutfetten (LDL-Apherese mit Dextransulfat-Absorption) können schwere Überempfindlichkeitsreaktionen bis hin zum lebensbedrohlichen Schock auslösen. Im Falle einer notfallmäßigen Blutwäsche oder Hämofiltration oder der Notwendigkeit einer LDL-Apherese muss deshalb vorher auf ein anderes für das betreffende Anwendungsgebiet geeignetes Arzneimittel – keinen ACE-Hemmer – umgestellt werden oder eine andere Dialysemembran verwendet werden. Teilen Sie Ihrem Arzt mit, dass Sie mit Enal behandelt werden bzw. Dialysen benötigen, damit der Arzt dies bei der Behandlung berücksichtigen kann.

Falls Sie vor einer Operation oder Narkose (auch beim Zahnarzt) stehen, teilen Sie Ihrem Arzt mit, dass Sie Enal einnehmen, da es unter der Narkose zu einem plötzlichen Blutdruckabfall kommen kann.

Informieren Sie sofort Ihren Arzt, falls bei Ihnen folgende Krankheitszeichen auftreten:
- Schwellung von Gesicht, Gliedmaßen, Lippen, Schleimhaut, Zunge und/oder Kehlkopf, Atemnot
- Gelbfärbung von Haut und Schleimhäuten
- Fieber, Lymphknotenschwellung und/oder Halsentzündung.

In diesen Fällen dürfen Sie Enal nicht weiter einnehmen und Ihr Arzt wird entsprechende Maßnahmen ergreifen.

Die Anwendung dieses Arzneimittels bedarf der regelmäßigen ärztlichen Kontrolle. Halten Sie daher bitte die vom Arzt angeordneten Laborkontrollen und Untersuchungen unbedingt ein.

Kinder
Die Daten zur Anwendung von Enalaprilmaleat bei Kindern mit Bluthochdruck sind begrenzt. Bezüglich der anderen Anwendungsgebiete gibt es keine Daten. Zur Anwendung von Enalprilmaleat liegen Daten zur Verträglichkeit und Wirksamkeit nur zu Anwendung von Enalaprilmaleat bei Kindern ab 6 Jahren in der Behandlung von Bluthochdruck vor, daher wird Enal für Kinder ausschließlich zur Behandlung dieser Erkrankung empfohlen.
Neugeborene und Kinder mit Nierenerkrankungen sollen nicht mit Enal behandelt werden.

Einnahme mit anderen Arzneimitteln
Informieren Sie Ihren Arzt oder Apotheker bei gleichzeitigem oder kürzlichem Gebrauch anderer Arzneimittel. Dies betrifft insbesondere:
- *Harntreibende Arzneimittel mit verminderter Kaliumausscheidung (kaliumsparende Diuretika) und Kaliumpräparate:*
  ACE-Hemmer mildern den Kaliumverlust durch harntreibende Arzneimittel. Bestimmte harntreibende Arzneimittel (kaliumsparende Diuretika, wie z. B. Spironolacton, Triamteren oder Amilorid), Kaliumpräparate, kaliumhaltige Salzersatzmittel oder Heparin (gerinnungshemmendes Arzneimittel) können zu einem deutlichen Anstieg des Kaliumwertes im Blut führen. Die gleichzeitige Anwendung sollte mit Vorsicht und unter häufiger Überprüfung der Kaliumwerte im Blut erfolgen.
- *Andere harntreibende Arzneimittel (Thiazide oder Schleifendiuretika):*
  Eine vorangegangene hoch dosierte Behandlung mit harntreibenden Arzneimitteln kann zu Volumenmangel und damit zum Risiko eines Blutdruckabfalls bei Therapiebeginn mit Enal führen. Die blutdrucksenkende Wirkung kann durch Absetzen des harntreibenden Arzneimittels, einem Ausgleich des Volumenmangels bzw. Gabe von Salz oder durch Einleitung der Therapie mit Enalaprilmaleat in niedriger Dosierung vermindert werden.
- *Andere blutdrucksenkende Arzneimittel (Antihypertensiva):*
  Die gleichzeitige Anwendung von Enal mit anderen blutdrucksenkenden Arzneimitteln kann die blutdrucksenkende Wirkung von Enal verstärken. Auch die gleichzeitige Anwendung von Nitroglyzerin und anderen Nitraten oder anderen gefäßerweiternd wirkenden Arzneimitteln (Vasodilatatoren) kann den Blutdruck weiter senken.
- *Lithium (Arzneimittel gegen Depressionen):*
  Unter der gleichzeitigen Anwendung von ACE-Hemmern und Lithium wurde über reversible Anstiege der Lithiumwerte im Blut und schädliche (toxische) Effekte berichtet. Eine gleichzeitige Therapie mit bestimmten harntreibenden Arzneimitteln (Thiaziddiuretika) kann die Lithium-Konzentration im Blut und damit das Risiko einer schädlichen Wirkung von Lithium unter einer ACE-Hemmer-Therapie erhöhen. Die Anwendung von Enal mit Lithium wird deshalb nicht empfohlen; sollte diese Kombination aber erforderlich sein, sind die Lithiumwerte im Blut sorgfältig zu überwachen.
- *Arzneimittel gegen Depressionen sowie gegen andere psychische Erkrankungen, Betäubungsmittel, Narkosemittel (trizyklische Antidepressiva, Neuroleptika, Anästhetika, Narkotika):*
  Eine gleichzeitige Anwendung mit ACE-Hemmern kann zu einer verstärkten Blutdrucksenkung führen.
- *Arzneimittel gegen Schmerzen und Entzündungen (nicht steroidale Antiphlogistika):*
  Die Dauertherapie mit Arzneimitteln gegen Schmerzen und Entzündungen kann die blutdrucksenkende Wirkung von ACE-Hemmern abschwächen. Eine gleichzeitige Behandlung kann zu einer Erhöhung der Kaliumwerte im Blut und zu einer Verschlechterung der Nierenfunktion führen, die gewöhnlich reversibel ist. Selten kann es auch zu akutem Nierenversagen kommen, insbesondere bei Patienten mit eingeschränkter Nierenfunktion z.B. bei älteren Patienten oder Patienten mit Flüssigkeitsmangel.
- *Sympathomimetika (Mittel, die ähnliche Wirkungen wie die körpereigenen Überträgerstoffe Noradrenalin bzw. Adrenalin hervorrufen, z. B. Blutdrucksteigerung):* Sympathomimetika können die blutdrucksenkende Wirkung von ACE-Hemmern abschwächen.
- *Blutzuckersenkende Arzneimittel und Insulin (Antidiabetika):*
  Bei gleichzeitiger Anwendung mit ACE-Hemmern kann es zu einer Verstärkung der blutzuckersenkenden Wirkung kommen; es besteht das Risiko, dass Blutzuckerwerte unter Normalwerte absinken (Hypoglykämie). Diese Fälle treten offenbar insbesondere in den ersten Wochen der kombinierten Behandlung sowie bei Patienten mit eingeschränkter Nierenfunktion auf.
- *Acetylsalicylsäure (Arzneimittel, das in niedriger Dosierung zum Schutz vor Herz-Kreislauf-Erkrankungen eingesetzt wird), Arzneimittel zur Auflösung von Blutgerinnseln (Thrombolytika), Betablocker (Arzneimittel z.B. zur Behandlung des Bluthochdrucks):*
  Eine gleichzeitige Behandlung mit Enal kann erfolgen.

Nahrungsmittel und Getränke
Die Nahrungsaufnahme hat keinen Einfluss auf die Aufnahme von Enal in den Körper. Alkohol verstärkt die blutdrucksenkende Wirkung von ACE-Hemmern.

Verkehrstüchtigkeit und Maschinen
Die Behandlung mit diesem Arzneimittel bedarf der regelmäßigen ärztlichen Kontrolle. Durch individuell auftretende unterschiedliche Reaktionen kann das Reaktionsvermögen soweit verändert sein, dass die Fähigkeit zur aktiven Teilnahme am Straßenverkehr, zum Bedienen von Maschinen oder zum Arbeiten ohne sicheren Halt beeinträchtigt wird. Dies gilt in verstärktem Maße bei Behandlungsbeginn, Dosiserhöhung und Präparatewechsel sowie im Zusammenwirken mit Alkohol.

3. Wie ist Enal einzunehmen?

Nehmen Sie Enal immer nach Anweisung Ihres Arztes ein.

Ihr Arzt wird Ihre anfängliche Dosis individuell nach Ihrem Gesundheitszustand und dem Schweregrad Ihrer Erkrankung wählen und entsprechend der Wirkung des Arzneimittels auf Ihren Blutdruck die Dosis schrittweise anpassen.

Bluthochdruck
Anfangsdosis:
Die Anfangsdosis beträgt 1-mal täglich 5 mg Enalaprilmaleat bis maximal 1-mal täglich 1 Tablette Enal (entsprechend 20 mg Enalaprilmaleat) je nach Schweregrad der Erkrankung und Ihrem Zustand.
- Leichter Bluthochdruck:
  Die empfohlene Anfangsdosis beträgt: 1-mal täglich 5 mg Enalaprilmaleat bis zu 10 mg Enalaprilmaleat täglich
- Patienten mit stark aktiviertem blutdruckregulierendem System z. B. bei Bluthochdruck aufgrund einer Nierenerkrankung, Salz- und/oder Flüssigkeitsmangel, nicht ausgeglichener Herzleistungsschwäche oder schwerem Bluthochdruck:
  Die Therapie wird mit 1-mal täglich 5 mg Enalaprilmaleat oder einer geringeren Dosis eingeleitet. Bei Therapiebeginn kann es zu einem übermäßigen Blutdruckabfall kommen; eine engmaschige ärztliche Überwachung ist erforderlich.
- Patienten mit vorausgegangener Therapie mit hoch dosierten harntreibenden Arzneimitteln (Diuretika):
  Die Therapie wird mit 1-mal täglich 5 mg Enalaprilmaleat oder einer geringeren Dosis eingeleitet.
  Eine vorausgegangene Therapie mit hoch dosierten harntreibenden Arzneimitteln kann zu einem Flüssigkeitsmangel führen, so dass die Gefahr eines Blutdruckabfalls bei Therapiebeginn besteht. Wenn möglich sollten diese Arzneimittel 2-3 Tage lang abgesetzt werden, bevor die Therapie mit Enal eingeleitet wird. Die Nierenfunktion und die Kaliumwerte im Blut sollten überwacht werden.

Erhaltungsdosis:
Die übliche Erhaltungsdosis beträgt 1-mal täglich 1 Tablette Enal (entsprechend 20 mg Enalaprilmaleat). Eine Tageshöchstdosis von 40 mg Enalaprilmaleat sollte nicht überschritten werden.
Für die niedrigeren Dosierungen stehen Tabletten mit geeigneter Wirkstoffstärke zur Verfügung.

Herzleistungsschwäche (symptomatische Herzinsuffizienz)/Funktionsstörung der linken Herzkammer (asymptomatische linksventrikuläre Dysfunktion)
Anfangsdosis:
Enal wird bei der Behandlung der Herzleistungsschwäche üblicherweise zusätzlich zu harntreibenden Arzneimitteln und Digitalis oder Betablockern angewendet.
Die Anfangsdosis beträgt 1-mal täglich 2,5 mg Enalaprilmaleat. Die Therapie ist unter engmaschiger ärztlicher Überwachung einzuleiten, um die anfängliche Wirkung auf den Blutdruck zu ermitteln.
Erhaltungsdosis:
Zu Beginn der Therapie mit Enal kann es bei Patienten mit Herzleistungsschwäche zu einem Blutdruckabfall kommen. Wenn dieser behoben ist, sollte die Dosis schrittweise über einen Zeitraum von 2-4 Wochen auf die Erhaltungsdosis von 20 mg Enalaprilmaleat täglich gesteigert werden. Diese Dosis kann als Einzeldosis eingenommen oder auf zwei Gaben verteilt werden, je nach Verträglichkeit.
Eine Tageshöchstdosis von 2-mal 1 Tablette Enal (entsprechend 40 mg Enalaprilmaleat), auf 2 Gaben verteilt, sollte nicht überschritten werden. Für die niedrigeren Dosierungen stehen Tabletten mit geeigneter Wirkstoffstärke zur Verfügung.
Sie sollten besonders vorsichtig sein, wenn Sie Ihre erste Dosis einnehmen oder wenn Ihre Dosis erhöht wird. Teilen Sie Ihrem Arzt unverzüglich mit, wenn Sie sich benommen oder schwindlig fühlen. Vor und nach Beginn der Einnahme von Enal sollten Blutdruck und Nierenfunktion engmaschig überwacht werden, da über Blutdruckabfall und (seltener) nachfolgendem Nierenversagen berichtet wurde. Wenn Sie mit harntreibenden Arzneimitteln behandelt werden, sollte – falls möglich – deren Dosis vor Beginn der Einnahme von Enal verringert werden. Ein Blutdruckabfall bei Therapiebeginn mit Enal bedeutet nicht, dass auch während der Dauerbehandlung mit Enal solche Reaktionen auftreten werden und schließt die Weiterbehandlung mit dem Arzneimittel nicht aus. Die Kaliumwerte im Blut und die Nierenfunktion sollten ebenfalls überwacht werden.

Eingeschränkte Nierenfunktion
Grundsätzlich sollten die Abstände zwischen den Anwendungen von Enal verlängert werden und/oder die Dosis reduziert werden. Ihr Arzt wird Ihre Behandlung individuell festlegen.
Bei mäßiger Einschränkung der Nierenfunktion wird eine Dosis von 1-mal täglich 5-10 mg Enalaprilmaleat empfohlen.
Bei schwerer Nierenfunktionseinschränkung wird eine Dosis von 1-mal täglich 2,5 mg Enalaprilmaleat empfohlen.
Für Dialysepatienten wird eine Dosis von 1-mal täglich 2,5 mg Enalaprilmaleat an Dialyse-Tagen empfohlen. An dialysefreien Tagen richtet sich die Dosis nach der Blutdrucksenkung.

Patienten über 65 Jahre
Die Dosis sollte sich nach der Nierenfunktion des Patienten richten.

Kinder unter 18 Jahre
Wenn die Kinder Tabletten schlucken können, wird die Dosis vom Arzt individuell dem Zustand des Kindes und der Blutdrucksenkung angepasst. Die empfohlene Anfangsdosis für Kinder mit Bluthochdruck und mit einem Gewicht von 20 kg bis 50 kg beträgt 1-mal täglich 2,5 mg Enalaprilmaleat; Kinder, die mehr als 50 kg wiegen, erhalten 1-mal täglich 5 mg Enalaprilmaleat. Die weitere Dosierung wird vom Arzt dem Bedarf des Kindes angepasst. Dabei darf eine Tageshöchstdosis von 20 mg Enalaprilmaleat für Kinder mit 20 kg bis 50 kg Körpergewicht bzw. 40 mg Enalaprilmaleat für Kinder mit mehr als 50 kg Körpergewicht nicht überschritten werden.
Neugeborene und Kinder mit Nierenerkrankungen sollen nicht mit Enal behandelt werden.

Art der Einnahme
Nehmen Sie die Tabletten unzerkaut mit ausreichend Flüssigkeit (z.B. einem Glas Wasser) ein. Die Einnahme kann unabhängig von den Mahlzeiten erfolgen. Die angegebene Tagesmenge wird in der Regel morgens auf einmal eingenommen, kann aber gegebenenfalls auch auf 2 Einnahmen morgens und abends verteilt werden.

Dauer der Einnahme
Die Dauer der Behandlung bestimmt Ihr Arzt. Die Behandlung mit Enal ist in der Regel eine Langzeittherapie.

Bei Einnahme von zu viel Enal
Wenn Sie durch ein Versehen zu viele Tabletten eingenommen haben oder ein Kind einige Tabletten geschluckt hat, wenden Sie sich sofort an einen Arzt/Notarzt. Dieser kann entsprechend der Schwere der Vergiftung über die erforderlichen Maßnahmen entscheiden.
In Abhängigkeit vom Ausmaß der Überdosierung sind folgende Symptome möglich:
Starker Blutdruckabfall, Kreislaufversagen, beschleunigter oder verlangsamter Herzschlag, Herzklopfen, Nierenversagen, Atembeschleunigung, Schwindel, Angstgefühl und Husten. Bei Verdacht auf eine Überdosierung benötigen Sie ärztliche Hilfe!

Bei vergessener Einnahme
Nehmen Sie beim nächsten Mal nicht zusätzlich mehr Tabletten ein, sondern setzen Sie die Einnahme von Enal wie verordnet fort.

Abbrechen der Einnahme
Unterbrechen oder beenden Sie die Behandlung mit Enal nicht ohne Rücksprache mit Ihrem behandelnden Arzt!
Bei Patienten mit Bluthochdruck kann der Blutdruck erneut ansteigen und bei Patienten mit Herzleistungsschwäche können die Symptome wieder auftreten.

4. Mögliche Nebenwirkungen
Studien belegen, dass bei korrektem Gebrauch von Enal der Nutzen überwiegt.

Häufigkeiten der Nebenwirkungen:
Sehr häufig, betrifft mehr als 1 von 10 Personen
- Verschwommensehen
- Schwindel
- Husten
- Übelkeit
- Schwächegefühl

Häufig, betrifft 1 bis 10 von 100 Personen
- Ausschlag, Überempfindlichkeit/Gewebeschwellung (**angioneurotisches Ödem**): angioneurotische Ödeme mit Beteiligung von Gesicht, Gliedmaßen, Lippen, Zunge, Stimmapparat des Kehlkopfes (Glottis) und/oder Kehlkopf wurden beobachtet.
  Eine Gewebeschwellung (angioneurotisches Ödem) mit Beteiligung von Kehlkopf, Stimmapparat des Kehlkopfes und/oder Zunge muss von Ihrem Arzt sofort mit Notfallmedikamenten behandelt werden.
- Kopfschmerzen, Depressionen
- Übermäßige Blutdrucksenkung einschließlich übermäßiger Blutdruckabfall bei Lagewechsel vom Liegen zum Stehen (orthostatische Hypotonie), kurzzeitiger Bewusstseinsverlust (Synkope), Herzinfarkt oder Schlaganfall, vermutlich infolge übermäßigen Blutruckabfalls bei gefährdeten Patienten (Patienten mit Durchblutungsstörungen im Bereich des Herzens und/oder des Gehirns), Schmerzen im Brustkorb, Herzrhythmusstörungen, Herzengegefühl (Angina pectoris), beschleunigter Herzschlag (Tachykardie).
- Atemnot (Dyspnoe)
- Durchfall, Bauchschmerzen, Geschmacksveränderungen.
- Müdigkeit
- Anstieg der Kaliumwerte im Blut, Anstieg der Kreatininwerte im Blut

Gelegentlich, betrifft 1 bis 10 von 1.000 Personen
- Blutarmut durch vermehrten Zerfall roter Blutkörperchen (hämolytische Anämie), Blutarmut durch Blutbildungsstörung im Knochenmark (aplastische Anämie)
- Zu niedrige Blutzuckerwerte (Hypoglykämie)
- Verwirrtheitszustände, Schläfrigkeit, Schlaflosigkeit, Nervosität, Missempfindungen (z.B. Kribbeln, pelziges Gefühl), Schwindel (Vertigo)
- Übermäßiger Blutdruckabfall bei Lagewechsel vom Liegen zum Stehen (orthostatische Hypotonie), Herzklopfen
- Verstärkte Schleimabsonderung aus der Nase (Rhinorrhö), Halsschmerzen und Heiserkeit, krampfartige Verengung der Bronchien (Bronchospasmus), Asthma
- Darmverschluss (Ileus), Entzündung der Bauchspeicheldrüse, Erbrechen, Verdauungsstörungen, Verstopfung, Appetitlosigkeit, Magenreizung, Mundtrockenheit, Magengeschwür (peptisches Ulkus)
- Vermehrtes Schwitzen, Juckreiz, Nesselsucht, Haarausfall
- Nierenfunktionsstörungen, Nierenversagen, vermehrte Eiweißausscheidung im Urin (Proteinurie)
- Impotenz
- Muskelkrämpfe, Gesichtsrötung (Flush), Ohrgeräusche (Tinnitus), Unwohlsein, Fieber
- Anstieg des Harnstoffs im Blut, Abnahme der Natriumwerte im Blut

Selten, betrifft 1 bis 10 von 10.000 Personen
- Verminderung der Anzahl bestimmter Blutzellen (Neutropenie, Thrombozytopenie, Panzytopenie) bis zu einer hochgradigen Verminderung bestimmter weißer Blutkörperchen mit Infektneigung und schweren Allgemeinsymptomen (Agranulozytose), Abnahme bestimmter Laborwerte (Hämoglobin und Hämatokrit), herabgesetzte Funktion des Knochenmarks (Knochenmarksdepression), Lymphknotenschwellung, Autoimmunkrankheiten
  Beim Auftreten von **Fieber, Lymphknotenschwellungen** und/oder **Halsentzündung** benachrichtigen Sie bitte umgehend Ihren Arzt, damit er das weiße Blutbild untersuchen kann.
- **Gelbsucht, erhöhte Leberwerte** (Leberenzyme, Serum-Bilirubin)
  Wenn bei Ihnen eine Gelbsucht auftritt oder die Leberenzymwerte bei Ihnen deutlich ansteigen, müssen Sie die Behandlung abbrechen, und Ihr Arzt wird Sie überwachen.
- **Schwerwiegende Hautreaktionen** (Erythema multiforme, Stevens-Johnson-Syndrom, exfoliative Dermatitis, toxische epidermale Nekrolyse, Pemphigus, Erythroderma)
  Falls Sie den Verdacht haben, dass sich bei Ihnen eine schwerwiegende Hautreaktion entwickelt, müssen Sie sofort Ihren Arzt aufsuchen und gegebenenfalls die Behandlung mit Enal abbrechen.
- Verändertes Träumen, Schlafstörungen
- Durch Gefäßkrämpfe bedingte Durchblutungsstörungen an Händen und Füßen (Raynaud-Phänomen)
- Auffälligkeiten im Lungengewebe (pulmonale Infiltrate), Schnupfen, allergische Entzündungen der Lunge (allergische Alveolitis / eosinophile Pneumonie)
- Entzündungen der Mundschleimhaut mit Geschwürbildung (Stomatitis/aphthöse Ulzerationen), Entzündungen der Zungenschleimhaut (Glossitis)
- Leberversagen, Leberentzündung (Hepatitis - hepatozellulär oder cholestatisch, einschließlich hepatische Nekrose)
- Verminderte Harnausscheidung (Oligurie)
- Vergrößerung der Brust bei Männern (Gynäkomastie)

Sehr selten, betrifft weniger als 1 von 10.000 Personen
- Gewebeschwellung des Darms (intestinales angioneurotisches Ödem)

Ein Symptomenkomplex wurde beschrieben, der mit einigen oder allen der folgenden Nebenwirkungen einhergehen kann: Fieber, Entzündung seröser Häute (Serositis), Gefäßentzündung (Vaskulitis), Muskel- und Gelenkschmerzen/Muskel- und Gelenkentzündungen (Myalgien/Myositis, Arthralgien/ Arthritis) und bestimmten Laborwertveränderungen (positive ANA-Titer, erhöhte Blutkörperchensenkungsgeschwindigkeit , Eosinophilie und Leukozytose). Hautausschlag, Lichtempfindlichkeit oder andere Reaktionen der Haut können auftreten.

Informieren Sie bei Nebenwirkungen immer den Arzt oder Apotheker.

5. Wie ist Enal aufzubewahren?
Für Kinder unzugänglich.
Sie dürfen das Arzneimittel nach dem auf dem Etikett oder dem Behältnis angegebenen Verfallsdatum nicht mehr anwenden.
Nicht über 25°C aufbewahren.

Enal ist nur für Sie verordnet. Geben Sie es nicht anderen Menschen, auch wenn diese ähnliche Beschwerden haben.

6. Weitere Information
Zusammensetzung
Eine Tablette enthält:
- wirksamer Bestandteil:
  20 mg Enalaprilmaleat
- weitere Bestandteile: Croscarmellose-Natrium, Eisenoxidhydrat (E 172), Eisen(III)-oxid (E 172), Lactose-Monohydrat, Magnesiumstearat (Ph.Eur.), Natriumhydrogencarbonat, vorverkleisterte Stärke (Mais).

Hersteller
SanFarma
Sonnenstraße 1
D-12345 Sonne
Tel: 0423/233345
Fax: 0423/23344
Sanfarma@info.de

Letzte Überarbeitung der Packungsbeilage
11/2011

Appendix 3: German BfArM text package leaflet with QRD template 7.3.1

GEBRAUCHSINFORMATION: INFORMATION FÜR DEN ANWENDER

Enal 20 mg Tabletten

Enalaprilmaleat

Lesen Sie die gesamte Packungsbeilage sorgfältig durch, bevor Sie mit der Einnahme dieses Arzneimittels beginnen.
- Heben Sie die Packungsbeilage auf. Vielleicht möchten Sie diese später nochmals lesen.
- Wenn Sie weitere Fragen haben, wenden Sie sich an Ihren Arzt oder Apotheker.
- Dieses Arzneimittel wurde Ihnen persönlich verschrieben. Geben Sie es nicht an Dritte weiter. Es kann anderen Menschen schaden, auch wenn diese die gleichen Beschwerden haben wie Sie.
- Wenn eine der aufgeführten Nebenwirkungen Sie erheblich beeinträchtigt oder Sie Nebenwirkungen bemerken, die nicht in dieser Gebrauchsinformation angegeben sind, informieren Sie bitte Ihren Arzt oder Apotheker.

Diese Packungsbeilage beinhaltet:

1. WAS IST ENAL UND WOFÜR WIRD ES ANGEWENDET?

Enal ist ein ACE-Hemmer, d. h. ein Arzneimittel mit blutdrucksenkenden und herzentlastenden Eigenschaften.

Enal wird angewendet:
- zur Behandlung eines hohen Blutdrucks (Hypertonie)
- zur Behandlung einer Herzleistungsschwäche (symptomatische Herzinsuffizienz)
- zur Vorbeugung der Entwicklung einer Herzleistungsschwäche (symptomatische Herzinsuffizienz) bei Patienten mit einer Funktionseinschränkung der linken Herzkammer, die noch keine Zeichen einer Herzleistungsschwäche verursacht (asymptomatische linksventrikuläre Dysfunktion mit einer linksventrikulären Auswurffraktion [LVEF] ≤ 35%).

2. WAS MÜSSEN SIE VOR DER EINNAHME VON ENAL BEACHTEN?

Enal darf nicht eingenommen werden,
- wenn Sie überempfindlich (allergisch) gegen Enalapril, einen anderen ACE-Hemmer oder einen der sonstigen Bestandteile von Enal sind.
- wenn bei Ihnen während einer früheren Behandlung mit einem ACE-Hemmer Gewebeschwellungen (angioneurotische Ödeme) auftraten
- wenn Sie eine vererbte Neigung zu Gewebeschwellungen oder Gewebeschwellungen aus unbekannter Ursache haben (hereditäres oder idiopathisches Angioödem)
- während der letzten 6 Monate der Schwangerschaft (Es wird empfohlen, Enal auch in der frühen Phase der Schwangerschaft nicht anzuwenden, siehe Abschnitt „Schwangerschaft und Stillzeit").

Besondere Vorsicht bei der Einnahme von Enal ist erforderlich,
- wenn bei Ihnen das Risiko eines übermäßigen Blutdruckabfalls besteht, weil Sie an Störungen des Salz- und Flüssigkeitshaushaltes leiden, z.B. weil Sie harntreibende Arzneimittel einnehmen oder eine salzarme Diät durchführen oder als Folge von Erbrechen oder Durchfall
- wenn die Herzklappen Ihrer linken Herzkammer verengt sind oder andere Ausflussbehinderungen aus der linken Herzkammer bestehen
- wenn Sie an einer Herzerkrankung mit Unterbrechung der Durchblutung (Ischämie) leiden
- wenn Sie an Durchblutungsstörungen des Gehirns (zerebrovaskuläre Erkrankung) leiden
- wenn Ihre Nierenfunktion eingeschränkt ist (Kreatinin-Clearance unter 80 ml/Minute)
- wenn bei Ihnen eine Einengung der Nierenschlagadern vorliegt (beidseitig bzw. einseitig bei Einzelniere)
- wenn bei Ihnen kürzlich eine Nierenverpflanzung durchgeführt wurde
- wenn bei Ihnen die Leberenzymwerte ansteigen oder Sie eine Gelbsucht entwickeln
- wenn bei Ihnen die Anzahl der weißen Blutkörperchen abnimmt (Leukopenie) bzw. sich eine hochgradige Verminderung bestimmter weißer Blutkörperchen mit Infektneigung und schweren Allgemeinsymptomen (Agranulozytose) entwickelt
- wenn Sie an einer bestimmten Erkrankung des Bindegewebes (Kollagenosen) mit Gefäßbeteiligung leiden
- wenn Sie mit Arzneimitteln behandelt werden, die Ihre Abwehrreaktionen unterdrücken
- wenn Sie gleichzeitig Allopurinol (Arzneimittel gegen Gicht), Procainamid (Arzneimittel gegen Herzrhythmusstörungen) oder Lithium (Arzneimittel gegen bestimmte Depressionen) einnehmen
- wenn bei Ihnen während der Behandlung mit Enal Überempfindlichkeitsreaktionen bzw. Gewebeschwellungen (Angioödeme) auftreten
- wenn Sie unter Zuckerkrankheit leiden (Diabetes mellitus)
- wenn bei Ihnen ein hartnäckiger, trockner Husten auftritt
- wenn bei Ihnen das Risiko einer Erhöhung der Kaliumwerte im Blut besteht
- wenn die Blutdrucksenkung aufgrund Ihrer ethnischen Zugehörigkeit (insbesondere bei Patienten mit schwarzer Hautfarbe) nicht ausreichend stark ist.

Wenn bei Ihnen eine Desensibilisierungstherapie gegen Insektengifte (z.B. von Bienen oder Wespen) notwendig ist, ist Enal vorübergehend durch ein geeignetes Arzneimittel aus einer anderen Stoffklasse zu ersetzen. Es können sonst lebensbedrohliche Überempfindlichkeitsreaktionen (z.B. Blutdruckabfall, Atemnot, Erbrechen, allergische Hautreaktionen) auftreten. Solche Reaktionen können auch nach Insektenstichen (von z.B. Bienen oder Wespen) vorkommen.

Die gleichzeitige Anwendung von Enal bei einer Blutwäsche (Dialyse) mit bestimmten Dialysemembranen (High-flux-Membranen) bzw. bei einer Behandlung von stark erhöhten Blutfetten (LDL-Apherese mit Dextransulfat-Absorption) können schwere Überempfindlichkeitsreaktionen bis hin zum lebensbedrohlichen Schock auslösen. Im Falle einer notfallmäßigen Blutwäsche oder Hämofiltration oder der Notwendigkeit einer LDL-Apherese muss deshalb vorher auf ein anderes für das betreffende Anwendungsgebiet geeignetes Arzneimittel – keinen ACE-Hemmer – umgestellt werden oder eine andere Dialysemembran verwendet werden.
Teilen Sie Ihrem Arzt mit, dass Sie mit Enal behandelt werden bzw. Dialysen benötigen, damit der Arzt dies bei der Behandlung berücksichtigen kann.

Falls Sie vor einer Operation oder Narkose (auch beim Zahnarzt) stehen, teilen Sie Ihrem Arzt mit, dass Sie Enal einnehmen, da es unter der Narkose zu einem plötzlichen Blutdruckabfall kommen kann.

Informieren Sie sofort Ihren Arzt, falls bei Ihnen folgende Krankheitszeichen auftreten:
- Schwellung von Gesicht, Gliedmaßen, Lippen, Schleimhaut, Zunge und/oder Kehlkopf, Atemnot
- Gelbfärbung von Haut und Schleimhäuten
- Fieber, Lymphknotenschwellung und/oder Halsentzündung.

In diesen Fällen dürfen Sie Enal nicht weiter einnehmen und Ihr Arzt wird entsprechende Maßnahmen ergreifen.

Die Anwendung dieses Arzneimittels bedarf der regelmäßigen ärztlichen Kontrolle. Halten Sie daher bitte die vom Arzt angeordneten Laborkontrollen und Untersuchungen unbedingt ein.

Kinder
Die Daten zur Anwendung von Enalaprilmaleat bei Kindern mit Bluthochdruck sind begrenzt. Bezüglich der anderen Anwendungsgebiete gibt es keine Daten. Zur Anwendung von Enalaprilmaleat liegen Daten zur Verträglichkeit und Wirksamkeit nur zu Anwendung von Enalaprilmaleat bei Kindern ab 6 Jahren in der Behandlung von Bluthochdruck vor, daher wird Enal für Kinder ausschließlich zur Behandlung dieser Erkrankung empfohlen.
Neugeborene und Kinder mit Nierenerkrankungen sollen nicht mit Enal behandelt werden.

Bei Einnahme von Enal mit anderen Arzneimitteln
Bitte informieren Sie Ihren Arzt oder Apotheker, wenn Sie andere Arzneimittel einnehmen bzw. vor kurzem eingenommen haben, auch wenn es sich um nicht verschreibungspflichtige Arzneimittel handelt.
Bei gleichzeitiger Einnahme von Enal und anderen Arzneimitteln ist insbesondere zu berücksichtigen:
- *Harntreibende Arzneimittel mit verminderter Kaliumausscheidung (kaliumsparende Diuretika) und Kaliumpräparate*
ACE-Hemmer mildern den Kaliumverlust durch harntreibende Arzneimittel. Bestimmte harntreibende Arzneimittel (kaliumsparende Diuretika, wie z. B. Spironolacton, Triamteren oder Amilorid), Kaliumpräparate, kaliumhaltige Salzersatzmittel oder Heparin (gerinnungshemmendes Arzneimittel) können zu einem deutlichen Anstieg des Kaliumwertes im Blut führen. Die gleichzeitige Anwendung sollte mit Vorsicht und unter häufiger Überprüfung der Kaliumwerte im Blut erfolgen.
- *Andere harntreibende Arzneimittel (Thiazide oder Schleifendiuretika):*
Eine vorangegangene hoch dosierte Behandlung mit harntreibenden Arzneimitteln kann zu Volumenmangel und damit zum Risiko eines Blutdruckabfalls bei Therapiebeginn mit Enal führen. Die blutdrucksenkende Wirkung kann durch Absetzen des harntreibenden Arzneimittels, einem Ausgleich des Volumenmangels bzw. Gabe von Salz oder durch Einleitung der Therapie mit Enalaprilmaleat in niedriger Dosierung vermindert werden.
- *Andere blutdrucksenkende Arzneimittel (Antihypertensiva):*
Die gleichzeitige Anwendung von Enal mit anderen blutdrucksenkenden Arzneimitteln kann die blutdrucksenkende Wirkung von Enal verstärken. Auch die gleichzeitige Anwendung von Nitroglycerin und anderen Nitraten oder anderen gefäßerweiternd wirkenden Arzneimitteln (Vasodilatatoren) kann den Blutdruck weiter senken.
- *Lithium (Arzneimittel gegen Depressionen):*
Unter der gleichzeitigen Anwendung von ACE-Hemmern und Lithium wurde über reversible Anstiege der Lithiumwerte im Blut und schädliche (toxische) Effekte berichtet. Eine gleichzeitige Therapie mit bestimmten harntreibenden Arzneimitteln (Thiaziddiuretika) kann die Lithium-Konzentration im Blut und damit das Risiko einer schädlichen Wirkung von Lithium unter einer ACE-Hemmer-Therapie erhöhen. Die Anwendung von Enal mit Lithium wird deshalb nicht empfohlen; sollte diese Kombination aber erforderlich sein, sind die Lithiumwerte im Blut sorgfältig zu überwachen.
- *Arzneimittel gegen Depressionen sowie gegen andere psychische Erkrankungen, Betäubungsmittel, Narkosemittel (trizyklische Antidepressiva, Neuroleptika, Anästhetika, Narkotika):*
Eine gleichzeitige Anwendung mit ACE-Hemmern kann zu einer verstärkten Blutdrucksenkung führen.
- *Arzneimittel gegen Schmerzen und Entzündungen (nicht steroidale Antiphlogistika):*
Die Dauertherapie mit Arzneimitteln gegen Schmerzen und Entzündungen kann die blutdrucksenkende Wirkung von ACE-Hemmern abschwächen. Eine gleichzeitige Behandlung kann zu einer Erhöhung der Kaliumwerte im Blut und zu einer Verschlechterung der Nierenfunktion führen, die gewöhnlich reversibel ist. Selten kann es auch zu akutem Nierenversagen kommen, insbesondere bei Patienten mit eingeschränkter Nierenfunktion z.B. bei älteren Patienten oder Patienten mit Flüssigkeitsmangel.
- *Sympathomimetika (Mittel, die ähnliche Wirkungen wie die körpereigenen Überträgerstoffe Noradrenalin bzw. Adrenalin hervorrufen, z.B. Blutdrucksteigerung)*
Sympathomimetika können die blutdrucksenkende Wirkung von ACE-Hemmern abschwächen.
- *Blutzuckersenkende Arzneimittel und Insulin (Antidiabetika):*
Bei gleichzeitiger Anwendung mit ACE-Hemmern kann es zu einer Verstärkung der blutzuckersenkenden Wirkung kommen; es besteht das Risiko, dass Blutzuckerwerte unter Normalwerte absinken (Hypoglykämie). Diese Fälle treten offenbar insbesondere in den ersten Wochen der kombinierten Behandlung sowie bei Patienten mit eingeschränkter Nierenfunktion auf.
- *Acetylsalicylsäure (Arzneimittel, das in niedriger Dosierung zum Schutz vor Herz-Kreislauf-Erkrankungen eingesetzt wird), Arzneimittel zur Auflösung von Blutgerinnseln (Thrombolytika), Betablocker (Arzneimittel z.B. zur Behandlung des Bluthochdrucks):*
Eine gleichzeitige Behandlung mit Enal kann erfolgen.

Bei Einnahme von Enal zusammen mit Nahrungsmitteln und Getränken
Die Nahrungsaufnahme hat keinen Einfluss auf die Aufnahme von Enal in den Körper. Alkohol verstärkt die blutdrucksenkende Wirkung von ACE-Hemmern.

Schwangerschaft und Stillzeit
Fragen Sie vor der Einnahme von allen Arzneimitteln Ihren Arzt oder Apotheker um Rat.

Schwangerschaft
Teilen Sie Ihrem Arzt mit, wenn Sie vermuten, schwanger zu sein oder schwanger werden könnten. In der Regel wird Ihr Arzt Ihnen empfehlen, Enal vor einer Schwangerschaft bzw. sobald Sie wissen, dass Sie schwanger sind, abzusetzen, und er wird Ihnen ein anderes Arzneimittel empfehlen. Die Anwendung von Enal in der frühen Schwangerschaft wird nicht empfohlen und Enal darf nicht mehr nach dem dritten Schwangerschaftsmonat eingenommen werden, da die Einnahme von Enal in diesem Stadium zu schweren Schädigungen Ihres ungeborenen Kindes führen kann.

Stillzeit
Teilen sie Ihrem Arzt mit, wenn Sie stillen oder mit dem Stillen beginnen wollen. Das Stillen von Neugeborenen (in den ersten Wochen nach der Geburt) und besonders von Frühgeburten wird nicht empfohlen, wenn Sie Enal einnehmen.
Bei älteren Säuglingen sollte der Arzt Sie über Nutzen und mögliche Schäden der Anwendung von Enal in der Stillzeit im Vergleich zu Behandlungsalternativen aufklären.

Verkehrstüchtigkeit und das Bedienen von Maschinen
Die Behandlung mit diesem Arzneimittel bedarf der regelmäßigen ärztlichen Kontrolle. Durch individuell auftretende unterschiedliche Reaktionen kann das Reaktionsvermögen soweit verändert sein, dass die Fähigkeit zur aktiven Teilnahme am Straßenverkehr, zum Bedienen von Maschinen oder zum Arbeiten ohne sicheren Halt beeinträchtigt wird. Dies gilt in verstärktem Maße bei Behandlungsbeginn, Dosiserhöhung und Präparatewechsel sowie im Zusammenwirken mit Alkohol.

Wichtige Informationen über bestimmte sonstige Bestandteile von Enal
Dieses Arzneimittel enthält Lactose. Bitte nehmen Sie es daher erst nach Rücksprache mit dem Arzt ein, wenn Ihnen bekannt ist, dass Sie unter einer Unverträglichkeit gegenüber bestimmten Zuckern leiden.

3. WIE IST ENAL EINZUNEHMEN?

Nehmen Sie Enal immer genau nach Anweisung des Arztes ein. Bitte fragen Sie bei Ihrem Arzt oder Apotheker nach, wenn Sie sich nicht ganz sicher sind. Falls vom Arzt nicht anders verordnet, ist die übliche Dosis:

Ihr Arzt wird Ihre anfängliche Dosis individuell nach Ihrem Gesundheitszustand und dem Schweregrad Ihrer Erkrankung wählen und entsprechend der Wirkung des Arzneimittels auf Ihren Blutdruck die Dosis schrittweise anpassen.

Bluthochdruck
Anfangsdosis:
Die Anfangsdosis beträgt 1-mal täglich 5 mg Enalaprilmaleat bis maximal 1-mal täglich 1 Tablette Enal (entsprechend 20 mg Enalaprilmaleat) je nach Schweregrad der Erkrankung und Ihrem Zustand.
- Leichter Bluthochdruck:
Die empfohlene Anfangsdosis beträgt: 1-mal täglich 5 mg Enalaprilmaleat bis zu 10 mg Enalaprilmaleat täglich.
- Patienten mit stark aktiviertem blutdruckregulierendem System z. B. bei Bluthochdruck aufgrund einer Nierenerkrankung, Salz- und/oder Flüssigkeitsmangel, nicht ausgeglichener Herzleistungsschwäche oder schwerem Bluthochdruck:
Die Therapie wird mit 1-mal täglich 5 mg Enalaprilmaleat oder einer geringeren Dosis eingeleitet. Bei Therapiebeginn kann es zu einem übermäßigen Blutdruckabfall kommen; eine engmaschige ärztliche Überwachung ist erforderlich.
- Patienten mit vorausgegangener Therapie mit hoch dosierten harn-treibenden Arzneimitteln (Diuretika):
Die Therapie wird mit 1-mal täglich 5 mg Enalaprilmaleat oder einer geringeren Dosis eingeleitet.
Eine vorausgegangene Therapie mit hoch dosierten harntreibenden Arzneimitteln kann zu einem Flüssigkeitsmangel führen, so dass die Gefahr eines Blutdruckabfalls bei Therapiebeginn besteht. Wenn möglich sollten diese Arzneimittel 2-3 Tage lang abgesetzt werden, bevor die Therapie mit Enal eingeleitet wird. Die Nierenfunktion und die Kaliumwerte im Blut sollten überwacht werden.

Erhaltungsdosis:
Die übliche Erhaltungsdosis beträgt 1-mal täglich 1 Tablette Enal (entsprechend 20 mg Enalaprilmaleat). Eine Tageshöchstdosis von 40 mg Enalaprilmaleat sollte nicht überschritten werden.
Für die niedrigeren Dosierungen stehen Tabletten mit geeigneter Wirkstoffstärke zur Verfügung.

Herzleistungsschwäche (symptomatische Herzinsuffizienz)/ Funktionsstörung der linken Herzkammer (asymptomatische linksventrikuläre Dysfunktion)
Anfangsdosis:
Enal wird bei der Behandlung der Herzleistungsschwäche üblicherweise zusätzlich zu harntreibenden Arzneimitteln und Digitalis oder Betablockern angewendet.
Die Anfangsdosis beträgt 1-mal täglich 2,5 mg Enalaprilmaleat.
Die Therapie ist unter engmaschiger ärztlicher Überwachung einzuleiten, um die anfängliche Wirkung auf den Blutdruck zu ermitteln.
Erhaltungsdosis:
Zu Beginn der Therapie mit Enal kann es bei Patienten mit Herzleistungsschwäche zu einem Blutdruckabfall kommen. Wenn dieser behoben ist, sollte die Dosis schrittweise über einen Zeitraum von 2-4 Wochen auf die Erhaltungsdosis von 20 mg Enalaprilmaleat täglich gesteigert werden. Diese Dosis kann als Einzeldosis eingenommen oder auf zwei Gaben verteilt werden, je nach Verträglichkeit.
Eine Tageshöchstdosis von 2-mal 1 Tablette Enal (entsprechend 40 mg Enalaprilmaleat), auf 2 Gaben verteilt, sollte nicht überschritten werden. Für die niedrigeren Dosierungen stehen Tabletten mit geeigneter Wirkstoffstärke zur Verfügung.

Sie sollten besonders vorsichtig sein, wenn Sie Ihre erste Dosis einnehmen oder wenn Ihre Dosis erhöht wird. Teilen Sie Ihrem Arzt unverzüglich mit, wenn Sie sich benommen oder schwindlig fühlen.
Vor und nach Beginn der Einnahme von Enal sollten Blutdruck und Nierenfunktion engmaschig überwacht werden, da über Blutdruckabfall und (seltener) nachfolgendem Nierenversagen berichtet wurde. Wenn Sie mit harntreibenden Arzneimitteln behandelt werden, sollte – falls möglich – deren Dosis vor Beginn der Einnahme von Enal verringert werden. Ein Blutdruckabfall bei Therapiebeginn mit Enal bedeutet nicht, dass auch während der Dauerbehandlung mit Enal solche Reaktionen auftreten werden und schließt die Weiterbehandlung mit dem Arzneimittel nicht aus. Die Kaliumwerte im Blut und die Nierenfunktion sollten ebenfalls überwacht werden.

Dosierung bei eingeschränkter Nierenfunktion
Grundsätzlich sollten die Abstände zwischen den Anwendungen von Enal verlängert werden und/oder die Dosis reduziert werden. Ihr Arzt wird Ihre Behandlung individuell festlegen.
Bei mäßiger Einschränkung der Nierenfunktion wird eine Dosis von 1-mal täglich 5-10 mg Enalaprilmaleat empfohlen.
Bei schwerer Nierenfunktionseinschränkung wird eine Dosis von 1-mal täglich 2,5 mg Enalaprilmaleat empfohlen.
Für Dialysepatienten wird eine Dosis von 1-mal täglich 2,5 mg Enalaprilmaleat an Dialyse-Tagen empfohlen. An dialysefreien Tagen richtet sich die Dosis nach der Blutdrucksenkung.

Dosierung bei älteren Patienten
Die Dosis sollte sich nach der Nierenfunktion des Patienten richten.

Anwendung bei Kindern und Jugendlichen
Wenn die Kinder Tabletten schlucken können, wird die Dosis vom Arzt individuell dem Zustand des Kindes und der Blutdrucksenkung angepasst. Die empfohlene Anfangsdosis für Kinder mit Bluthochdruck und mit einem Gewicht von 20 kg bis 50 kg beträgt 1-mal täglich 2,5 mg Enalaprilmaleat; Kinder, die mehr als 50 kg wiegen, erhalten 1-mal täglich 5 mg Enalaprilmaleat. Die weitere Dosierung wird vom Arzt dem Bedarf des Kindes angepasst. Dabei darf eine Tageshöchstdosis von 20 mg Enalaprilmaleat für Kinder mit 20 kg bis 50 kg Körpergewicht bzw. 40 mg Enalaprilmaleat für Kinder mit mehr als 50 kg Körpergewicht nicht überschritten werden.
Neugeborene und Kinder mit Nierenerkrankungen sollen nicht mit Enal behandelt werden.

Nehmen Sie die Tabletten unzerkaut mit ausreichend Flüssigkeit (z.B. einem Glas Wasser) ein. Die Einnahme kann unabhängig von den Mahlzeiten erfolgen. Die angegebene Tagesmenge wird in der Regel morgens auf einmal eingenommen, kann aber gegebenenfalls auch auf 2 Einnahmen morgens und abends verteilt werden.

Die Dauer der Behandlung bestimmt Ihr Arzt. Die Behandlung mit Enal ist in der Regel eine Langzeittherapie.

Wenn Sie eine größere Menge von Enal eingenommen haben, als Sie sollten
Wenn Sie durch ein Versehen zu viele Tabletten eingenommen haben oder ein Kind einige Tabletten geschluckt hat, wenden Sie sich sofort an einen Arzt/Notarzt. Dieser kann entsprechend der Schwere der Vergiftung über die erforderlichen Maßnahmen entscheiden. In Abhängigkeit vom Ausmaß der Überdosierung sind folgende Symptome möglich:
Starker Blutdruckabfall, Kreislaufversagen, beschleunigter oder verlangsamter Herzschlag, Herzklopfen, Nierenversagen, Atembeschleunigung, Schwindel, Angstgefühl und Husten. Bei Verdacht auf eine Überdosierung benötigen Sie ärztliche Hilfe!

Wenn Sie die Einnahme von Enal vergessen haben
Nehmen Sie nicht die doppelte Dosis ein, wenn Sie die vorherige Einnahme vergessen haben, sondern setzen Sie die Einnahme von Enal wie verordnet fort.

Wenn Sie die Einnahme von Enal abbrechen
Unterbrechen oder beenden Sie die Behandlung mit Enal nicht ohne Rücksprache mit Ihrem behandelnden Arzt!
Bei Patienten mit Bluthochdruck kann der Blutdruck erneut ansteigen und bei Patienten mit Herzleistungsschwäche können die Symptome wieder auftreten.

Wenn Sie weitere Fragen zur Anwendung des Arzneimittels haben, fragen Sie Ihren Arzt oder Apotheker.

4. WELCHE NEBENWIRKUNGEN SIND MÖGLICH?

Wie alle Arzneimittel kann Enal Nebenwirkungen haben, die aber nicht bei jedem auftreten müssen.
Unerwünschte Wirkungen, die von Enal oder anderen ACE-Hemmern bekannt sind, finden Sie nachfolgend.

Bei der Bewertung von Nebenwirkungen werden folgende Häufigkeitsangaben zugrunde gelegt:

Sehr häufig	mehr als 1 von 10 Behandelten
Häufig	weniger als 1 von 10, aber mehr als 1 von 100 Behandelten
Gelegentlich	weniger als 1 von 100, aber mehr als 1 von 1000 Behandelten
Selten	weniger als 1 von 1000, aber mehr als 1 von 10.000 Behandelten
Sehr selten	weniger als 1 von 10.000 Behandelten, oder unbekannt

Sehr häufige Nebenwirkungen
- Verschwommensehen
- Schwindel
- Husten
- Übelkeit
- Schwächegefühl

Häufige Nebenwirkungen
- Kopfschmerzen, Depressionen
- Übermäßige Blutdrucksenkung einschließlich übermäßiger Blutdruckabfall bei Lagewechsel vom Liegen zum Stehen (orthostatische Hypotonie), kurzzeitiger Bewusstseinsverlust (Synkope), Herzinfarkt oder Schlaganfall, vermutlich infolge übermäßigen Blutdruckabfalls bei gefährdeten Patienten (Patienten mit Durchblutungsstörungen im Bereich des Herzens und/oder des Gehirns), Schmerzen im Brustkorb, Herzrhythmusstörungen, Herzengegefühl (Angina pectoris), beschleunigter Herzschlag (Tachykardie).
- Atemnot (Dyspnoe)
- Durchfall, Bauchschmerzen, Geschmacksveränderungen.
- Ausschlag, Überempfindlichkeit/Gewebeschwellung (angioneurotisches Ödem): angioneurotische Ödeme mit Beteiligung von Gesicht, Gliedmaßen, Lippen, Zunge, Stimmapparat des Kehlkopfes (Glottis) und/oder Kehlkopf wurden beobachtet.
- Müdigkeit
- Anstieg der Kaliumwerte im Blut, Anstieg der Kreatininwerte im Blut.

Gelegentliche Nebenwirkungen
- Blutarmut durch vermehrten Zerfall roter Blutkörperchen (hämolytische Anämie), Blutarmut durch Blutbildungsstörung im Knochenmark (aplastische Anämie)
- Zu niedrige Blutzuckerwerte (Hypoglykämie)
- Verwirrtheitszustände, Schläfrigkeit, Schlaflosigkeit, Nervosität, Missempfindungen (z.B. Kribbeln, pelziges Gefühl), Schwindel (Vertigo)
- Übermäßiger Blutdruckabfall bei Lagewechsel vom Liegen zum Stehen (orthostatische Hypotonie), Herzklopfen
- Verstärkte Schleimabsonderung aus der Nase (Rhinorrhö), Halsschmerzen und Heiserkeit, krampfartige Verengung der Bronchien (Bronchospasmus), Asthma
- Darmverschluss (Ileus), Entzündung der Bauchspeicheldrüse, Erbrechen, Verdauungsstörungen, Verstopfung, Appetitlosigkeit, Magenreizung, Mundtrockenheit, Magengeschwür (peptisches Ulkus)
- Vermehrtes Schwitzen, Juckreiz, Nesselsucht, Haarausfall
- Nierenfunktionsstörungen, Nierenversagen, vermehrte Eiweißausscheidung im Urin (Proteinurie)
- Impotenz
- Muskelkrämpfe, Gesichtsrötung (Flush), Ohrgeräusche (Tinnitus), Unwohlsein, Fieber
- Anstieg des Harnstoffs im Blut, Abnahme der Natriumwerte im Blut

Seltene Nebenwirkungen
- Verminderung der Anzahl bestimmter Blutzellen (Neutropenie, Thrombozytopenie, Panzytopenie) bis zu einer hochgradigen Verminderung bestimmter weißer Blutkörperchen mit Infektneigung und schweren Allgemeinsymptomen (Agranulozytose), Abnahme bestimmter Laborwerte (Hämoglobin und Hämatokrit), herabgesetzte Funktion des Knochenmarks (Knochenmarksdepression), Lymphknotenschwellung, Autoimmunkrankheiten
- Verändertes Träumen, Schlafstörungen
- Durch Gefäßkrämpfe bedingte Durchblutungsstörungen an Händen und Füßen (Raynaud-Phänomen)
- Auffälligkeiten im Lungengewebe (pulmonale Infiltrate), Schnupfen, allergische Entzündungen der Lunge (allergische Alveolitis / eosinophile Pneumonie)
- Entzündungen der Mundschleimhaut mit Geschwürbildung (Stomatitis/aphthöse Ulzerationen), Entzündungen der Zungenschleimhaut (Glossitis)
- Leberversagen, Leberentzündung (Hepatitis - hepatocellulär oder cholestatisch, einschließlich hepatische Nekrose), Gelbsucht
- Schwerwiegende Hautreaktionen (Erythema multiforme, Stevens-Johnson-Syndrom, exfoliative Dermatitis, toxische epidermale Nekrolyse, Pemphigus, Erythroderma)
- Verminderte Harnausscheidung (Oligurie)
- Vergrößerung der Brust bei Männern (Gynäkomastie)
- Erhöhte Leberwerte (Leberenzyme, Serum-Bilirubin)

Sehr seltene Nebenwirkungen
- Gewebeschwellung des Darms (intestinales angioneurotisches Ödem)

Ein Symptomenkomplex wurde beschrieben, der mit einigen oder allen der folgenden Nebenwirkungen einhergehen kann: Fieber, Entzündung seröser Häute (Serositis), Gefäßentzündung (Vaskulitis), Muskel- und Gelenkschmerzen/Muskel- und Gelenkentzündungen (Myalgien/Myositis, Arthralgien/Arthritis) und bestimmten Laborwertveränderungen (positive ANA-Titer, erhöhte Blutkörperchensenkungsgeschwindigkeit, Eosinophilie und Leukozytose). Hautausschlag, Lichtempfindlichkeit oder andere Reaktionen der Haut können auftreten.

Gegenmaßnahmen
Falls Sie den Verdacht haben, dass sich bei Ihnen eine schwerwiegende Hautreaktion entwickelt, müssen Sie sofort Ihren Arzt aufsuchen und gegebenenfalls die Behandlung mit Enal abbrechen.
Eine Gewebeschwellung (angioneurotisches Ödem) mit Beteiligung von Kehlkopf, Stimmapparat des Kehlkopfes und/oder Zunge muss von Ihrem Arzt sofort mit Notfallmedikamenten behandelt werden.
Wenn bei Ihnen eine Gelbsucht auftritt oder die Leberenzymwerte bei Ihnen deutlich ansteigen, müssen Sie die Behandlung abbrechen, und Ihr Arzt wird Sie überwachen.
Beim Auftreten von Fieber, Lymphknotenschwellungen und/oder Halsentzündung benachrichtigen Sie bitte umgehend Ihren Arzt, damit er das weiße Blutbild untersuchen kann.
Sollten Sie die oben genannten Nebenwirkungen bei sich beobachten, benachrichtigen Sie Ihren Arzt. Er wird über den Schweregrad und gegebenenfalls über erforderliche weitere Maßnahmen entscheiden.

Informieren Sie bitte Ihren Arzt oder Apotheker, wenn eine der aufgeführten Nebenwirkungen Sie erheblich beeinträchtigt oder Sie Nebenwirkungen bemerken, die nicht in dieser Gebrauchsinformation angegeben sind.

5. WIE IST ENAL AUFZUBEWAHREN?

Arzneimittel für Kinder unzugänglich aufbewahren!
Sie dürfen das Arzneimittel nach dem auf dem Etikett oder dem Behältnis nach EXP angegebenen Verfalldatum nicht mehr anwenden. Das Verfalldatum bezieht sich auf den letzten Tag des Monats.
Nicht über 25°C aufbewahren.
Das Arzneimittel darf nicht im Abwasser oder Haushaltsabfall entsorgt werden. Fragen Sie Ihren Apotheker wie das Arzneimittel zu entsorgen ist, wenn Sie es nicht mehr benötigen. Diese Maßnahme hilft die Umwelt zu schützen.

6. WEITERE INFORMATIONEN

Was Enal enthält:
- Der Wirkstoff ist: Enalaprilmaleat. Eine Tablette enthält 20 mg Enalaprilmaleat.
- Die sonstigen Bestandteile sind: Croscarmellose-Natrium, Eisenoxidhydrat (E 172), Eisen(III)-oxid (E 172), Lactose-Monohydrat, Magnesiumstearat (Ph.Eur.), Natriumhydrogencarbonat, vorverkleisterte Stärke (Mais).

Wie Enal aussieht und Inhalt der Packung:
Runde, gelbliche Tablette; Packungen mit 30, 50 und 100 Tabletten.

Pharmazeutischer Unternehmer und Hersteller
SanFarma
Sonnenstraße 1
D-12345 Sonne
Tel: 0423/233345
Fax: 0423/233344
Sanfarma@info.de

Falls weitere Informationen über das Arzneimittel gewünscht werden, setzen Sie sich bitte mit dem örtlichen Vertreter des Pharmazeutischen Unternehmers in Verbindung.

België/Belgique/Belgien
SanFarma S.A.
Rue de La Monnaie 24
B-1500 Bruxelles
Tél/Tel: + 32 (0) 800 56 456
SFBelgium_info@sanfarma.com

България
ЗАНФАРМА
Bul. Todor Silvnista Г
ЯВГМ София
Тел.: + 359 4567656
info-sf@sanfarma.com

Česká republika
SanFarma Pharmaceuticals CR
Moskevská 7
CZ Praha
Tel: +420 255366
sfarma_cr@sanfarma.com

Danmark
SanFarma Denmark A/S
Tarp Hovedvej 12
DK-5277 Esbjerg
Tlf: + 45 567893
info_dk@sanfarma.com

Deutschland
SanFarma
Sonnenstraße 1
D-12345 Sonne
Tel: + 49 (0) 423/233345
Sanfarma@info.de

Eesti
SanFarma Baltics Eesti Filiaal
Tallskivi plats 3
EE – 10564 Kesklinn
Tel: +372 667523
Sanfarmaeesti@sanfarma.com

Ελλάδα
SanFarma Ελλάς
Λιοσιών
GR-457 77 Πολυμάζ
Τηλ: + 30 5669 222
info@sanfarma.gr

España
SanFarma S.L.U.
Calle de los Filato 12
E-75421 Montilla del Palancar
Tel: + 34 5669 111
info@sanfarma.es

France
SanFarma France
Rue de la Loire 34
F-24985 Tours
Tél: + 33 (0) 25 665544
contact@sanfarma-france.com

Ireland
SanFarma Ireland
89 Dromore Street
IRL - Banbridge BT34 5JH
Tel: + 353 (0) 5662333
info_ireland@sanfarma.com

Ísland
SanFarma
Tjarnagata 78
IS-105 Reykjavík
Sími: + 354 5622366
isregulatory@sanfarma.com

Italia
SanFarma Italy S.p.A.
Via Tuscolana 33
I-54896 Roma
Tel: + 39 (0) 3562 112
info@s-farma.com

Κύπρος
SanFarma Ελλάς
Σπηλιά
CY-000 00 Γερίου
Τηλ: + 30 45433 11
cyprus_info@sanfarma.com

Latvija
SanFarma Latvijā
Liela Iela 44
Jelgava, LV-1256
Tel: + 371 453 222
Info_lv@sanfarma.com

Lietuva
SanFarma Baltics
Perkūno alėja 44
LT 44301 Kaunas
Tel: +370 564 232
info_lietuva@sanfarma.com

Luxembourg/Luxemburg
SanFarma S.A.
Route d'Esch 66
L-1510 Luxembourg
Tél/Tel: + 32 (0) 800 56 456
SFBelgium_info@sanfarma.com

Magyarország
SanFarma Magyarország Zrt
Attila híd 8
H-5688 Budapest
Tel.: + 36 569 599
service.hungary@sanfarma.com

Malta
SanFarma Ελλάς
Triq Il-Konti 666
MT-4596 San Qormi
Tel: + 356 234588
info_malta@sfarma.com

Nederland
SanFarma Nederland B.V.
De la Meppelweg 25
NL-5663 AA Den Haag
Tel: + 31 (0) 453 1199
info.sanfarma-nl@sanfarma.com

Norge
SanFarma Norway A.S.
Grünerløkka 3
N-9548 Oslo
Tlf: + 47 254 923
info.sanfarma@sanfarma.com

Österreich
SanFarma Generics
Nußdorfer Straße 33
A-2156 Wien
Tel: + 43 (0) 456 11888
Sanfarma@info.de

Polska
SanFarma Polska Sp.
Wyszogrodzka 2
PL – 77 455 Plock
Tel.: + 48 55 69971
sanfarmapolska@sanfarma.com

Portugal
SanFarma Farmacêuticos
São Domingo de Pedreira 578
P-4958-257 Odivelas
Tel: + 351 5956 223
informacao@sanfarma.com

România
SanFarma Pharmaceuticals
Strada Lungă 44
Sibiu 560220 – RO
Tel: + 40 200 551
sanfarmaromania@sanfarma.com

Slovenija
SanFarma d.d.
Trešnjevka-sjever 3
SI-1000 Zagreb
Tel: + 386 5623 66
sanfarma_slovenia@sanfarma.com

Slovenská republika
SanFarma Slovakia
Hlavná 2599/11
SK-070 02 Prešov
Tel: + 421 45213665
sanfarma_sk@sanfarma.com

Suomi/Finland
SanFarma Oy
Tapparakatu 166
FIN-80512 Juensuu
Puh/Tel: + 358 45657
info_dk@sanfarma.com

Sverige
SanFarma
Vaksealgatan 34
S-256 22 Uppsala
Tel: + 46 (0) 12345646
info_dk@sanfarma.com

United Kingdom
SanFarma UK
49 Walton Street
Oxford OX3 2JH UK
Tel: + 44 (0) 1856 2311
drugsafety@sanfarma.co.uk

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Ausführliche Informationen zu diesem Arzneimittel sind auf der Website der Europäischen Arzneimittel-Agentur http://www.ema.europa.eu/ verfügbar. Es gibt auch Links zu anderen Websites über seltene Erkrankungen und Behandlungen.

Appendix 4: German BfArM text package leaflet with QRD template 8

Gebrauchsinformation: Information für Patienten

Enal 20 mg Tabletten

Enalaprilmaleat

Lesen Sie die gesamte Packungsbeilage sorgfältig durch, bevor Sie mit der Einnahme dieses Arzneimittels beginnen, denn sie enthält wichtige Informationen.
- Heben Sie die Packungsbeilage auf. Vielleicht möchten Sie diese später nochmals lesen.
- Wenn Sie weitere Fragen haben, wenden Sie sich an Ihren Arzt, Apotheker oder Ihre Pflegekraft.
- Dieses Arzneimittel wurde Ihnen persönlich verschrieben. Geben Sie es nicht an Dritte weiter. Es kann anderen Menschen schaden, auch wenn diese die gleichen Beschwerden haben wie Sie.
- Wenn Sie Nebenwirkungen bemerken, wenden Sie sich an Ihren Arzt, Apotheker oder Ihre Pflegefachkraft. Dies gilt auch für Nebenwirkungen, die nicht in dieser Packungsbeilage angegeben sind.

Was in dieser Packungsbeilage steht

1. Was ist Enal und wofür wird es angewendet?

Enal enthält Enalapril. Es ist ein ACE-Hemmer, d.h. ein Arzneimittel mit blutdrucksenkenden und herzentlastenden Eigenschaften.

Enal wird angewendet:
- zur Behandlung eines hohen Blutdrucks (Hypertonie)
- zur Behandlung einer Herzleistungsschwäche (symptomatische Herzinsuffizienz)
- zur Vorbeugung der Entwicklung einer Herzleistungsschwäche (symptomatische linksventrikuläre Dysfunktion mit einer linksventrikulären Auswurffraktion (LVEF) ≤ 35%).

Dieses Arzneimittel bewirkt eine Blutdrucksenkung, was hilfreich zur Vorbeugung von Komplikationen durch erhöhten Blutdruck ist.

2. Was sollten Sie vor der Einnahme von Enal beachten?

Enal darf nicht eingenommen werden
- wenn Sie allergisch gegen Enalapril, einen anderen ACE-Hemmer oder einen der in Abschnitt 6. genannten sonstigen Bestandteile dieses Arzneimittels sind.
- wenn bei Ihnen während einer früheren Behandlung mit einem ACE-Hemmer Gewebeschwellungen (angioneurotische Ödeme) auftraten
- wenn Sie eine vererbte Neigung zu Gewebeschwellungen oder Gewebeschwellungen aus unbekannter Ursache haben (hereditäres oder idiopathisches Angioödem)
- während der letzten 6 Monate der Schwangerschaft (Es wird empfohlen, Enal auch in der frühen Phase der Schwangerschaft nicht anzuwenden, siehe Abschnitt „Schwangerschaft und Stillzeit").

Warnhinweise und Vorsichtsmaßnahmen

Bitte sprechen Sie mit Ihrem Arzt, Apotheker oder Ihrer Pflegefachkraft, bevor Sie Enal einnehmen,
- wenn bei Ihnen das Risiko eines übermäßigen Blutdruckabfalls besteht, weil Sie an Störungen des Salz- und Flüssigkeitshaushaltes leiden, z.B. weil Sie harntreibende Arzneimittel einnehmen oder eine salzarme Diät durchführen oder als Folge von Erbrechen oder Durchfall
- wenn die Herzklappen Ihrer linken Herzkammer verengt sind oder andere Ausflussbehinderungen aus der linken Herzkammer bestehen
- wenn Sie an einer Herzerkrankung mit Unterbrechung der Durchblutung (Ischämie) leiden
- wenn Sie an Durchblutungsstörungen des Gehirns (zerebrovaskuläre Erkrankung) leiden
- wenn Ihre Nierenfunktion eingeschränkt ist (Kreatinin-Clearance unter 80 ml/Minute)
- wenn bei Ihnen eine Einengung der Nierenschlagadern vorliegt (beidseitig bzw. einseitig bei Einzelniere)
- wenn bei Ihnen kürzlich eine Nierenverpflanzung durchgeführt wurde
- wenn bei Ihnen die Leberenzymwerte ansteigen oder Sie eine Gelbsucht entwickeln
- wenn bei Ihnen die Anzahl der weißen Blutkörperchen abnimmt (Leukopenie) bzw. sich eine hochgradige Verminderung bestimmter weißer Blutkörperchen mit Infektneigung und schweren Allgemeinsymptomen (Agranulozytose) entwickelt
- wenn Sie an einer bestimmten Erkrankung des Bindegewebes (Kollagenosen) mit Gefäßbeteiligung leiden
- wenn Sie mit Arzneimitteln behandelt werden, die Ihre Abwehrreaktionen unterdrücken
- wenn Sie gleichzeitig Allopurinol (Arzneimittel gegen Gicht), Procainamid (Arzneimittel gegen Herzrhythmusstörungen) oder Lithium (Arzneimittel gegen bestimmte Depressionen) einnehmen
- wenn bei Ihnen während der Behandlung mit Enal Überempfindlichkeitsreaktionen bzw. Gewebeschwellungen (Angioödeme) auftreten
- wenn Sie unter Zuckerkrankheit leiden (Diabetes mellitus)
- wenn bei Ihnen ein hartnäckiger trockner Husten auftritt
- wenn bei Ihnen das Risiko einer Erhöhung der Kaliumwerte im Blut besteht
- wenn die Blutdrucksenkung aufgrund Ihrer ethnischen Zugehörigkeit (insbesondere bei Patienten mit schwarzer Hautfarbe) nicht ausreichend stark ist.

Wenn bei Ihnen eine Desensibilisierungstherapie gegen Insektengifte (z.B. von Bienen oder Wespen) notwendig ist, ist Enal vorübergehend durch ein geeignetes Arzneimittel aus einer anderen Stoffklasse zu ersetzen. Es können sonst lebensbedrohliche Überempfindlichkeitsreaktionen (z.B. Blutdruckabfall, Atemnot, Erbrechen, allergische Hautreaktionen) auftreten. Solche Reaktionen können auch nachStichen/Stichen (von z.B. Bienen oder Wespen) vorkommen.

Die gleichzeitige Anwendung von Enal bei einer Blutwäsche (Dialyse) mit bestimmten Dialysemembranen (High-flux-Membranen) bzw. bei einer Behandlung von stark erhöhten Blutfetten (LDL-Apherese mit Dextransulfat-Absorption) können schwere Überempfindlichkeitsreaktionen bis hin zum lebensbedrohlichen Schock auslösen. Im Falle einer notfallmäßigen Blutwäsche oder Hämofiltration oder der Notwendigkeit einer LDL-Apherese muss deshalb vorher auf ein anderes für das betreffende Anwendungsgebiet geeignetes Arzneimittel – keinen ACE-Hemmer – umgestellt werden oder eine andere Dialysemembran verwendet werden.
Teilen Sie Ihrem Arzt mit, dass Sie mit Enal behandelt werden bzw. Dialysen benötigen, damit der Arzt dies bei der Behandlung berücksichtigen kann.

Falls Sie vor einer Operation oder Narkose (auch beim Zahnarzt) stehen, teilen Sie Ihrem Arzt mit, dass Sie Enal einnehmen, da es unter der Narkose zu einem plötzlichen Blutdruckabfall kommen kann.

Informieren Sie sofort Ihren Arzt, falls bei Ihnen folgende Krankheitszeichen auftreten:
- Schwellung von Gesicht, Gliedmaßen, Lippen, Schleimhaut, Zunge und/oder Kehlkopf, Atemnot
- Gelbfärbung von Haut und Schleimhäuten
- Fieber, Lymphknotenschwellung und/oder Halsentzündung.

In diesen Fällen dürfen Sie Enal nicht weiter einnehmen und Ihr Arzt wird entsprechende Maßnahmen ergreifen.

Die Anwendung dieses Arzneimittels bedarf der regelmäßigen ärztlichen Kontrolle. Halten Sie daher bitte die vom Arzt angeordneten Laborkontrollen und Untersuchungen unbedingt ein.

Kinder und Jugendliche

Die Daten zur Anwendung von Enalaprilmaleat bei Kindern mit Bluthochdruck sind begrenzt. Bezüglich der anderen Anwendungsgebiete gibt es keine Daten. Zur Anwendung von Enalaprilmaleat liegen Daten zur Verträglichkeit und Wirksamkeit nur zu Anwendung von Enalaprilmaleat bei Kindern ab 6 Jahren in der Behandlung von Bluthochdruck vor, daher wird Enal für Kinder ausschließlich zur Behandlung dieser Erkrankung empfohlen.
Neugeborene und Kinder mit Nierenerkrankungen sollen nicht mit Enal behandelt werden.

Einnahme von Enal zusammen mit anderen Arzneimitteln

Informieren Sie Ihren Arzt oder Apotheker wenn Sie andere Arzneimittel einnehmen, kürzlich andere Arzneimittel eingenommen haben oder beabsichtigen andere Arzneimittel einzunehmen.

Bei gleichzeitiger Einnahme von Enal und anderen Arzneimitteln ist insbesondere zu berücksichtigen:
- *Harntreibende Arzneimittel mit verminderter Kaliumausscheidung (kaliumsparende Diuretika) und Kaliumpräparate:*
  ACE-Hemmer mildern den Kaliumverlust durch harntreibende Arzneimittel. Bestimmte harntreibende Arzneimittel (kaliumsparende Diuretika, wie z. B. Spironolacton, Triamteren oder Amilorid), Kaliumpräparate, kaliumhaltige Salzersatzmittel oder Heparin (gerinnungshemmendes Arzneimittel) können zu einem deutlichen Anstieg des Kaliumwertes im Blut führen. Die gleichzeitige Anwendung sollte mit Vorsicht und unter häufiger Überprüfung der Kaliumwerte im Blut erfolgen.
- *Andere harntreibende Arzneimittel (Thiazide oder Schleifendiuretika):*
  Eine vorangegangene hoch dosierte Behandlung mit harntreibenden Arzneimitteln kann zu Volumenmangel und damit zum Risiko eines Blutdruckabfalls bei Therapiebeginn mit Enal führen. Die blutdrucksenken-de Wirkung kann durch Absetzen des harntreibenden Arzneimittels, einem Ausgleich des Volumenmangels bzw. Gabe von Salz oder durch Einleitung der Therapie mit Enalaprilmaleat in niedriger Dosierung vermindert werden.
- *Andere blutdrucksenkende Arzneimittel (Antihypertensiva):*
  Die gleichzeitige Anwendung von Enal mit anderen blutdrucksenkenden Arzneimitteln kann die blutdrucksenkende Wirkung von Enal verstärken. Auch die gleichzeitige Anwendung von Nitroglyzerin und anderen Nitraten oder anderen gefäßerweiternd wirkenden Arzneimitteln (Vasodilatatoren) kann den Blutdruck weiter senken.
- *Lithium (Arzneimittel gegen Depressionen):*
  Unter der gleichzeitigen Anwendung von ACE-Hemmern und Lithium wurde über reversible Anstiege der Lithiumwerte im Blut und schädliche (toxische) Effekte berichtet. Eine gleichzeitige Therapie mit bestimmten harntreibenden Arzneimitteln (Thiaziddiuretika) kann die Lithium-Konzentration im Blut und damit das Risiko einer schädlichen Wirkung von Lithium unter einer ACE-Hemmer-Therapie erhöhen. Die Anwendung von Enal mit Lithium wird deshalb nicht empfohlen; sollte diese Kombination aber erforderlich sein, sind die Lithiumwerte im Blut sorgfältig zu überwachen.
- *Arzneimittel gegen Depressionen sowie gegen andere psychische Erkrankungen, Betäubungsmittel, Narkosemittel (trizyklische Antidepressiva, Neuroleptika, Anästhetika, Narkotika):*
  Eine gleichzeitige Anwendung mit ACE-Hemmern kann zu einer verstärkten Blutdrucksenkung führen.
- *Arzneimittel gegen Schmerzen und Entzündungen (nicht steroidale Antiphlogistika):*
  Die Dauertherapie mit Arzneimitteln gegen Schmerzen und Entzündungen kann die blutdrucksenkende Wirkung von ACE-Hemmern abschwächen. Eine gleichzeitige Behandlung kann zu einer Erhöhung der Kaliumwerte im Blut und zu einer Verschlechterung der Nierenfunktion führen, die gewöhnlich reversibel ist. Selten kann es auch zu akutem Nierenversagen kommen, insbesondere bei Patienten mit eingeschränkter Nierenfunktion z.B. bei älteren Patienten oder Patienten mit Flüssigkeitsmangel.
- *Sympathomimetika (Mittel, die ähnliche Wirkungen wie die körpereigenen Überträgerstoffe Noradrenalin bzw. Adrenalin hervorrufen, z. B. Blutdrucksteigerung):* Sympathomimetika können die blutdrucksenkende Wirkung von ACE-Hemmern abschwächen.
- *Blutzuckersenkende Arzneimittel und Insulin (Antidiabetika):*
  Bei gleichzeitiger Anwendung mit ACE-Hemmern kann es zu einer Verstärkung der blutzuckersenkenden Wirkung kommen; es besteht das Risiko, dass Blutzuckerwerte unter Normalwerte absinken (Hypoglykämie). Diese Fälle treten offenbar insbesondere in den ersten Wochen der kombinierten Behandlung sowie bei Patienten mit eingeschränkter Nierenfunktion auf.
- *Acetylsalicylsäure (Arzneimittel, das in niedriger Dosierung zum Schutz vor Herz-Kreislauf-Erkrankungen eingesetzt wird), Arzneimittel zur Auflösung von Blutgerinnseln (Thrombolytika), Betablocker (Arzneimittel z.B. zur Behandlung des Bluthochdrucks):*
  Eine gleichzeitige Behandlung mit Enal kann erfolgen.

Einnahme von Enal zusammen mit Nahrungsmitteln, Getränken und Alkohol

Die Nahrungsaufnahme hat keinen Einfluss auf die Aufnahme von Enal in den Körper. Alkohol verstärkt die blutdrucksenkende Wirkung von ACE-Hemmern.

Schwangerschaft, Stillzeit und Zeugungs-/Gebärfähigkeit

Wenn Sie schwanger sind oder stillen, oder wenn Sie vermuten, schwanger zu sein oder beabsichtigen, schwanger zu werden, fragen Sie vor der Einnahme dieses Arzneimittels Ihren Arzt oder Apotheker um Rat.

Schwangerschaft
Teilen Sie Ihrem Arzt mit, wenn Sie vermuten, schwanger zu sein oder schwanger werden könnten. In der Regel wird Ihr Arzt Ihnen empfehlen, Enal vor einer Schwangerschaft bzw. sobald Sie wissen, dass Sie schwanger sind, abzusetzen, und er wird Ihnen ein anderes Arzneimittel empfehlen. Die Anwendung von Enal in der frühen Schwangerschaft wird nicht empfohlen und Enal darf nicht mehr nach dem dritten Schwangerschaftsmonat eingenommen werden, da die Einnahme von Enal in diesem Stadium zu schweren Schädigungen Ihres ungeborenen Kindes führen kann.

Stillzeit
Teilen Sie Ihrem Arzt mit, wenn Sie stillen oder mit dem Stillen beginnen wollen. Das Stillen von Neugeborenen (in den ersten Wochen nach der Geburt) und besonders von Frühgeburten wird nicht empfohlen, wenn Sie Enal einnehmen.
Bei älteren Säuglingen sollte der Arzt Sie über Nutzen und mögliche Schäden der Anwendung von Enal in der Stillzeit im Vergleich zu Behandlungsalternativen aufklären.

Verkehrstüchtigkeit und Fähigkeit zum Bedienen von Maschinen

Die Behandlung mit diesem Arzneimittel bedarf der regelmäßigen ärztlichen Kontrolle. Durch individuell auftretende unterschiedliche Reaktionen kann das Reaktionsvermögen soweit verändert sein, dass die Fähigkeit zur aktiven Teilnahme am Straßenverkehr, zum Bedienen von Maschinen oder zum Arbeiten ohne sicheren Halt beeinträchtigt wird. Dies gilt in verstärktem Maße bei Behandlungsbeginn, Dosiserhöhung und Präparatewechsel sowie im Zusammenwirken mit Alkohol.

Enal enthält Lactose

Bitte nehmen Sie es daher erst nach Rücksprache mit dem Arzt ein, wenn Ihnen bekannt ist, dass Sie unter einer Unverträglichkeit gegenüber bestimmten Zuckern leiden.

3. Wie ist Enal einzunehmen?

Nehmen Sie dieses Arzneimittel immer genau nach Absprache mit Ihrem Arzt oder Apotheker ein. Fragen Sie bei Ihrem Arzt oder Apotheker nach, wenn Sie sich nicht sicher sind.
Die empfohlene Dosis beträgt:
Ihr Arzt wird Ihre anfängliche Dosis individuell nach Ihrem Gesundheitszustand und dem Schweregrad Ihrer Erkrankung wählen und entsprechend der Wirkung des Arzneimittels auf Ihren Blutdruck die Dosis schrittweise anpassen.

Bluthochdruck

Anfangsdosis:
Die Anfangsdosis beträgt 1-mal täglich 5 mg Enalaprilmaleat bis maximal 1-mal täglich 1 Tablette Enal (entsprechend 20 mg Enalaprilmaleat) je nach Schweregrad der Erkrankung und Ihrem Zustand.
- Leichter Bluthochdruck:
  Die empfohlene Anfangsdosis beträgt: 1-mal täglich 5 mg Enalaprilmaleat bis zu 10 mg Enalaprilmaleat täglich.
- Patienten mit stark aktiviertem blutdruckregulierendem System z. B. bei Bluthochdruck aufgrund einer Nierenerkrankung, Salz- und/oder Flüssigkeitsmangel, nicht ausgeglichener Herzleistungsschwäche oder schwerem Bluthochdruck:
  Die Therapie wird mit 1-mal täglich 5 mg Enalaprilmaleat oder einer geringeren Dosis eingeleitet. Bei Therapiebeginn kann es zu einem übermäßigen Blutdruckabfall kommen; eine engmaschige ärztliche Überwachung ist erforderlich.
- Patienten mit vorausgegangener Therapie mit hoch dosierten harn-treibenden Arzneimitteln (Diuretika):
  Die Therapie wird mit 1-mal täglich 5 mg Enalaprilmaleat oder einer geringeren Dosis eingeleitet.
  Eine vorausgegangene Therapie mit hoch dosierten harntreibenden Arzneimitteln kann zu einem Flüssigkeitsmangel führen, so dass die Gefahr eines Blutdruckabfalls bei Therapiebeginn besteht. Wenn möglich sollten diese Arzneimittel 2-3 Tage lang abgesetzt werden, bevor die Therapie mit Enal eingeleitet wird. Die Nierenfunktion und die Kaliumwerte im Blut sollten überwacht werden.

Erhaltungsdosis:
Die übliche Erhaltungsdosis beträgt 1-mal täglich 1 Tablette Enal (entsprechend 20 mg Enalaprilmaleat). Eine Tageshöchstdosis von 40 mg Enalaprilmaleat sollte nicht überschritten werden.
Für die niedrigeren Dosierungen stehen Tabletten mit geeigneter Wirkstoffstärke zur Verfügung.

Herzleistungsschwäche (symptomatische Herzinsuffizienz)/Funktionsstörung der linken Herzkammer (asymptomatische linksventrikuläre Dysfunktion)

Anfangsdosis:
Enal wird bei der Behandlung der Herzleistungsschwäche üblicherweise zusätzlich zu harntreibenden Arzneimitteln und Digitalis oder Betablockern angewendet.
Die Anfangsdosis beträgt 1-mal täglich 2,5 mg Enalaprilmaleat. Die Therapie ist unter engmaschiger ärztlicher Überwachung einzuleiten, um die anfängliche Wirkung auf den Blutdruck zu ermitteln.
Erhaltungsdosis:
Zu Beginn der Therapie mit Enal kann es bei Patienten mit Herzleistungsschwäche zu einem Blutdruckabfall kommen. Wenn dieser behoben ist, sollte die Dosis schrittweise über einen Zeitraum von 2-4 Wochen auf die Erhaltungsdosis von 20 mg Enalaprilmaleat täglich gesteigert werden. Diese Dosis kann als Einzeldosis eingenommen oder auf zwei Gaben verteilt werden, je nach Verträglichkeit.
Eine Tageshöchstdosis von 2-mal 1 Tablette Enal (entsprechend 40 mg Enalaprilmaleat), auf 2 Gaben verteilt, sollte nicht überschritten werden. Für die niedrigeren Dosierungen stehen Tabletten mit geeigneter Wirkstoffstärke zur Verfügung.

Sie sollten besonders vorsichtig sein, wenn Sie Ihre erste Dosis einnehmen oder wenn Ihre Dosis erhöht wird. Teilen Sie Ihrem Arzt unverzüglich mit, wenn Sie sich benommen oder schwindlig fühlen. Vor und nach Beginn der Einnahme von Enal sollten Blutdruck und Nierenfunktion engmaschig überwacht werden, da über Blutdruckabfall und (seltener) nachfolgendem Nierenversagen berichtet wurde. Wenn Sie mit harntreibenden Arzneimitteln behandelt werden, sollte – falls möglich – deren Dosis vor Beginn der Einnahme von Enal verringert werden. Ein Blutdruckabfall bei Therapiebeginn mit Enal bedeutet nicht, dass auch während der Dauerbehandlung mit Enal solche Reaktionen auftreten werden und schließt die Weiterbehandlung mit dem Arzneimittel nicht aus. Die Kaliumwerte im Blut und die Nierenfunktion sollten ebenfalls überwacht werden.

Dosierung bei eingeschränkter Nierenfunktion
Grundsätzlich sollten die Abstände zwischen den Anwendungen von Enal verlängert werden und/oder die Dosis reduziert werden.
Ihr Arzt wird Ihre Behandlung individuell festlegen.
Bei mäßiger Einschränkung der Nierenfunktion wird eine Dosis von 1-mal täglich 5-10 mg Enalaprilmaleat empfohlen.
Bei schwerer Nierenfunktionseinschränkung wird eine Dosis von 1-mal täglich 2,5 mg Enalaprilmaleat empfohlen.
Für Dialysepatienten wird eine Dosis von 1-mal täglich 2,5 mg Enalaprilmaleat an Dialyse-Tagen empfohlen. An dialysefreien Tagen richtet sich die Dosis nach der Blutdrucksenkung.

Dosierung bei älteren Patienten
Die Dosis sollte sich nach der Nierenfunktion des Patienten richten.

Anwendung bei Kindern und Jugendlichen
Wenn die Kinder Tabletten schlucken können, wird die Dosis vom Arzt individuell dem Zustand des Kindes und der Blutdrucksenkung angepasst. Die empfohlene Anfangsdosis für Kinder mit Bluthochdruck und mit einem Gewicht von 20 kg bis 50 kg beträgt 1-mal täglich 2,5 mg Enalaprilmaleat; Kinder, die mehr als 50 kg wiegen, erhalten 1-mal täglich 5 mg Enalaprilmaleat. Die weitere Dosierung wird vom Arzt dem Bedarf des Kindes angepasst. Dabei darf eine Tageshöchstdosis von 20 mg Enalaprilmaleat für Kinder mit 20 kg bis 50 kg Körpergewicht bzw. 40 mg Enalaprilmaleat für Kinder mit mehr als 50 kg Körpergewicht nicht überschritten werden.
Neugeborene und Kinder mit Nierenerkrankungen sollen nicht mit Enal behandelt werden.

Art der Einnahme
Nehmen Sie die Tabletten unzerkaut mit ausreichend Flüssigkeit (z.B. einem Glas Wasser) ein. Die Einnahme kann unabhängig von den Mahlzeiten erfolgen. Die angegebene Tagesmenge wird in der Regel morgens auf einmal eingenommen, kann aber gegebenenfalls auch auf 2 Einnahmen morgens und abends verteilt werden.
Die Tablette kann in gleiche Dosen geteilt werden.

Dauer der Einnahme
Die Dauer der Behandlung bestimmt Ihr Arzt. Die Behandlung mit Enal ist in der Regel eine Langzeittherapie.

Wenn Sie eine größere Menge von Enal eingenommen haben, als Sie sollten
Wenn Sie durch ein Versehen zu viele Tabletten eingenommen haben oder ein Kind einige Tabletten geschluckt hat, wenden Sie sich sofort an einen Arzt/Notarzt. Dieser kann entsprechend der Schwere der Vergiftung über die erforderlichen Maßnahmen entscheiden.
In Abhängigkeit vom Ausmaß der Überdosierung sind folgende Symptome möglich:
Starker Blutdruckabfall, Kreislaufversagen, beschleunigter oder verlangsamter Herzschlag, Herzklopfen, Nierenversagen, Atembeschleunigung, Schwindel, Angstgefühl und Husten. Bei Verdacht auf eine Überdosierung benötigen Sie ärztliche Hilfe!

Wenn Sie die Einnahme von Enal vergessen haben
Nehmen Sie nicht die doppelte Menge ein, wenn Sie die vorherige Einnahme vergessen haben.

Wenn Sie die Einnahme von Enal abbrechen
Unterbrechen oder beenden Sie die Behandlung mit Enal nicht ohne Rücksprache mit Ihrem behandelnden Arzt!
Bei Patienten mit Bluthochdruck kann der Blutdruck erneut ansteigen und bei Patienten mit Herzleistungsschwäche können die Symptome wieder auftreten.

Wenn Sie weitere Fragen zur Einnahme dieses Arzneimittels haben, wenden Sie sich an Ihren Arzt, Apotheker oder Ihre Pflegefachkraft.

4. Welche Nebenwirkungen sind möglich?

Wie alle Arzneimittel kann auch dieses Arzneimittel Nebenwirkungen haben, die aber nicht bei jedem auftreten müssen.
Unerwünschte Wirkungen, die von Enal oder anderen ACE-Hemmern bekannt sind, finden Sie nachfolgend.

Häufig: kann bis zu 1 von 10 Personen betreffen
- Überempfindlichkeit/Gewebeschwellung (**angioneurotisches Ödem**): angioneurotische Ödeme mit Beteiligung von Gesicht, Gliedmaßen, Lippen, Zunge, Stimmapparat des Kehlkopfes (Glottis) und/oder Kehlkopf wurden beobachtet.
  Eine Gewebeschwellung (angioneurotisches Ödem) mit Beteiligung von Kehlkopf, Stimmapparat des Kehlkopfes und/oder Zunge muss von Ihrem Arzt sofort mit Notfallmedikamenten behandelt werden.

Selten: kann bis zu 1 von 1.000 Personen betreffen
- Verminderung der Anzahl bestimmter Blutzellen (Neutropenie, Thrombozytopenie, Panzytopenie) bis zu einer hochgradigen Verminderung bestimmter weißer Blutkörperchen mit Infektneigung und schweren Allgemeinsymptomen (Agranulozytose)
  Beim Auftreten von Fieber, Lymphknotenschwellungen und/oder Halsentzündung benachrichtigen Sie bitte umgehend Ihren Arzt, damit er das weiße Blutbild untersuchen kann.
- Gelbsucht, erhöhte Leberwerte (Leberenzyme, Serum-Bilirubin)
  Wenn bei Ihnen eine Gelbsucht auftritt oder die Leberenzymwerte bei Ihnen deutlich ansteigen, müssen Sie die Behandlung abbrechen, und Ihr Arzt wird Sie überwachen.
- Schwerwiegende Hautreaktionen (Erythema multiforme, Stevens-Johnson-Syndrom, exfoliative Dermatitis, toxische epidermale Nekrolyse, Pemphigus, Erythrodermie)
  Falls Sie den Verdacht haben, dass sich bei Ihnen eine schwerwiegende Hautreaktion entwickelt, müssen Sie sofort Ihren Arzt aufsuchen und gegebenenfalls die Behandlung mit Enal abbrechen.

Sollten Sie die oben genannten Nebenwirkungen bei sich beobachten, benachrichtigen Sie Ihren Arzt. Er wird über den Schweregrad und gegebenenfalls über erforderliche weitere Maßnahmen entscheiden.

Weitere Nebenwirkungen:
Sehr häufig: kann mehr als 1 von 10 Personen betreffen
- Verschwommensehen
- Schwindel
- Husten
- Übelkeit
- Schwächegefühl

Häufig: kann bis zu 1 von 10 Personen betreffen
- Kopfschmerzen, Depressionen
- Übermäßige Blutdrucksenkung einschließlich übermäßiger Blutdruckabfall bei Lagewechsel vom Liegen zum Stehen (orthostatische Hypotonie), kurzzeitiger Bewusstseinsverlust (Synkope), Herzinfarkt oder Schlaganfall, vermutlich infolge übermäßigen Blutdruckabfalls bei gefährdeten Patienten (Patienten mit Durchblutungsstörungen im Bereich des Herzens und/oder des Gehirns), Schmerzen im Brustkorb, Herzrhythmusstörungen, Herzengegefühl (Angina pectoris), beschleunigter Herzschlag (Tachykardie).
- Atemnot (Dyspnoe)
- Durchfall, Bauchschmerzen, Geschmacksveränderungen.
- Ausschlag
- Müdigkeit
- Anstieg der Kaliumwerte im Blut, Anstieg der Kreatininwerte im Blut

Gelegentlich: kann bis zu 1 von 100 Personen betreffen
- Blutarmut durch vermehrten Zerfall roter Blutkörperchen (hämolytische Anämie), Blutarmut durch Blutbildungsstörung im Knochenmark (aplastische Anämie)
- Zu niedrige Blutzuckerwerte (Hypoglykämie)
- Verwirrtheitszustände, Schläfrigkeit, Schlaflosigkeit, Nervosität, Missempfindungen (z.B. Kribbeln, pelziges Gefühl), Schwindel (Vertigo)
- Übermäßiger Blutdruckabfall bei Lagewechsel vom Liegen zum Stehen (orthostatische Hypotonie), Herzklopfen
- Verstärkte Schleimabsonderung aus der Nase (Rhinorrhö), Halsschmerzen und Heiserkeit, krampfartige Verengung der Bronchien (Bronchospasmus), Asthma
- Darmverschluss (Ileus), Entzündung der Bauchspeicheldrüse, Erbrechen, Verdauungsstörungen, Verstopfung, Appetitlosigkeit, Magenreizung, Mundtrockenheit, Magengeschwür (peptisches Ulkus)
- Vermehrtes Schwitzen, Juckreiz, Nesselsucht, Haarausfall
- Nierenfunktionsstörungen, Nierenversagen, vermehrte Eiweißausscheidung im Urin (Proteinurie)
- Impotenz
- Muskelkrämpfe, Gesichtsrötung (Flush), Ohrgeräusche (Tinnitus), Unwohlsein, Fieber
- Anstieg des Harnstoffs im Blut, Abnahme der Natriumwerte im Blut

Selten: kann bis zu 1 von 1.000 Personen betreffen
- Abnahme bestimmter Laborwerte (Hämoglobin und Hämatokrit), herabgesetzte Funktion des Knochenmarks (Knochenmarksdepression), Lymphknotenschwellung, Autoimmunkrankheiten
- Verändertes Träumen, Schlafstörungen
- Durch Gefäßkrämpfe bedingte Durchblutungsstörungen an Händen und Füßen (Raynaud-Phänomen)
- Auffälligkeiten im Lungengewebe (pulmonale Infiltrate), Schnupfen, allergische Entzündungen der Lunge (allergische Alveolitis/eosinophile Pneumonie)
- Entzündungen der Mundschleimhaut mit Geschwürbildung (Stomatitis/aphthöse Ulzerationen), Entzündungen der Zungenschleimhaut (Glossitis)
- Leberversagen, Leberentzündung (Hepatitis - hepatozellulär oder cholestatisch, einschließlich hepatische Nekrose)
- Verminderte Harnausscheidung (Oligurie)
- Vergrößerung der Brust bei Männern (Gynäkomastie)

Sehr selten: kann bis zu 1 von 10.000 Personen betreffen
- Gewebeschwellung des Darms (intestinales angioneurotisches Ödem)

Ein Symptomenkomplex wurde beschrieben, der mit einigen oder allen der folgenden Nebenwirkungen einhergehen kann: Fieber, Entzündung seröser Häute (Serositis), Gefäßentzündung (Vaskulitis), Muskel- und Gelenkschmerzen/Muskel- und Gelenkentzündungen (Myalgien/Myositis, Arthralgien/Arthritis) und bestimmten Laborwertveränderungen (positive ANA-Titer, erhöhte Blutkörperchensenkungsgeschwindigkeit, Eosinophilie und Leukozytose). Hautausschlag, Lichtempfindlichkeit oder andere Reaktionen der Haut können auftreten.

Wenn Sie Nebenwirkungen bemerken, wenden Sie sich an Ihren Arzt, Apotheker oder Ihre Pflegefachkraft. Dies gilt auch für Nebenwirkungen, die nicht in dieser Packungsbeilage angegeben sind.

5. Wie ist Enal aufzubewahren?

Bewahren Sie dieses Arzneimittel für Kinder unzugänglich auf.
Sie dürfen das Arzneimittel nach dem auf dem Etikett oder dem Behältnis nach EXP angegebenen Verfalldatum nicht mehr anwenden. Das Verfalldatum bezieht sich auf den letzten Tag des Monats.
Nicht über 25°C aufbewahren.
Entsorgen Sie Arzneimittel nicht im Abwasser oder Haushaltsabfall. Fragen Sie Ihren Apotheker, wie das Arzneimittel zu entsorgen ist, wenn Sie es nicht mehr verwenden. Sie tragen damit zum Schutz der Umwelt bei.

6. Inhalt der Packung und weitere Informationen

Was Enal enthält:
- Der Wirkstoff ist: Enalaprilmaleat. Eine Tablette enthält 20 mg Enalaprilmaleat.
- Die sonstigen Bestandteile sind: Croscarmellose-Natrium, Eisenoxidhydrat (E 172), Eisen(III)-oxid (E 172), Lactose-Monohydrat, Magnesiumstearat (Ph.Eur.), Natriumhydrogencarbonat, vorverkleisterte Stärke (Mais).

Wie Enal aussieht und Inhalt der Packung
Runde, gelbliche Tabletten; Packungen mit 30, 50 und 100 Tabletten.

Pharmazeutischer Unternehmer und Hersteller
SanFarma
Sonnenstraße 1
D-12345 Sonne
Tel: 0423/233345
Fax: 0423/23344
Sanfarma@info.de

Falls Sie weitere Informationen über das Arzneimittel wünschen, setzen Sie sich bitte mit dem örtlichen Vertreter des pharmazeutischen Unternehmers in Verbindung.

België/Belgique/Belgien
SanFarma S.A
Rue de La Monnaie 24
B-1500 Bruxelles
Tél/Tel: + 32 (0) 800 56 456
SFBelgium_info@sanfarma.com

България
ЗАНФАРМА
Бул. Тодор Живков 1
1618 София
Тел.: + 359 4567656
info-sf@sanfarma.com

Česká republika
SanFarma Pharmaceuticals CR
Moskevská 7
CZ Praha
Tel: +420 255366
sfarma_cr@sanfarma.com

Danmark
SanFarma Denmark A/S
Tarp Hovedvej 12
DK-8277 Esbjerg
Tlf: + 45 567893
info_dk@sanfarma.com

Deutschland
SanFarma
Sonnenstraße 1
D-12345 Sonne
Tel: + 49 (0) 423/233345
Sanfarma@info.de

Eesti
SanFarma Baltics Eesti Filiaal
Telliskivi plats 3
EE – 10564 Kesklinn
Tel: +372 567523
Sanfarmaeesti@sanfarma.com

Ελλάδα
SanFarma Ελλάς
Λιμάνι Ζέας
GR-457 77 Παλαιμάς
Τηλ: + 30 5669 222
info@sanfarma.gr

España
SanFarma S.L.U.
Calle de los Riato 12
E-75421 Montilla del Palancar
Tel: + 34 5669 111
info@sanfarma.es

France
SanFarma France
Rue de la Loire 34
F-24985 Tours
Tél: + 33 (0) 25 665544
contact@sanfarma-france.com

Ireland
SanFarma Ireland
89 Dromore Street
IRL - Banbridge BT34 5JH
Tel: + 353 (0) 5662333
info_Ireland@sanfarma.com

Ísland
SanFarma
Tjarnagata 78
IS-105 Reykjavík
Sími: + 354 5622366
isregulatory@sanfarma.com

Italia
SanFarma Italy S.p.A.
Via Toscolana 33
I-54896 Roma
Tel: + 39 (0) 3562 112
info@s-farma.com

Κύπρος
SanFarma Ελλάς
Σπύρου Κυπριανού
CY-000 00 Γερμασόγεια
Τηλ: + 30 45433 11
cyprus_info@sanfarma.com

Latvija
SanFarma Latvijā
Liela iela 44
Jelgava, LV-1256
Tel: + 371 453 222
Info_lv@sanfarma.com

Lietuva
SanFarma Baltics
Perkūno alėja 44
LT 44301 Kaunas
Tel: +370 564 232
info_lietuva@sanfarma.com

Luxembourg/Luxemburg
SanFarma S.A.
Route d'Eich 66
L-1510 Luxembourg
Tél/Tel: + 32 (0) 800 56 456
SFBelgium_info@sanfarma.com

Magyarország
SanFarma Magyarország Zrt
Attila hid 8
H-5698 Budapest
Tel.: + 36 569 599
service.hungary@sanfarma.com

Malta
SanFarma Ελλάς
Triq Il-Konti 666
MT-4596 San Qormi
Tel: + 356 234588
Info_malta@sfarma.com

Nederland
SanFarma Nederland B.V.
De la Meppelweg 25
NL-5663 AA Den Haag
Tel: + 31 (0) 453 1189
info.sanfarma-nl@sanfarma.com

Norge
SanFarma Norway A.S.
Grünerløkka 3
N-9548 Oslo
Tlf: + 47 254 923
info.sanfarma@sanfarma.com

Österreich
SanFarma Generics
Nußdorfer Straße 33
A-2156 Wien
Tel: + 43 (0) 456 11888
Sanfarma@info.de

Polska
SanFarma Polska Sp.
Wyszogrodzka 2
PL – 77 455 Plock
Tel.: + 48 55 69971
sanfarmapolska@sanfarma.com

Portugal
SanFarma Farmacêuticos
São Domingo de Pedreira 578
P-4958-257 Odivelas
Tel: + 351 5956 223
informacao@sanfarma.com

România
SanFarma Pharmaceuticals
Strada Lungă 44
Sibiu 560220 – RO
Tel: + 40 200 551
sanfarmaromania@sanfarma.com

Slovenija
SanFarma d.d.
Trebinjeva-ijever 3
SI-1000 Zagreb
Tel: + 386 5623 66
sanfarma_slovenia@sanfarma.com

Slovenská republika
SanFarma Slovakia
Hlavná 2566/11
SK-070 02 Prešov
Tel: + 421 45213965
sanfarma_sk@sanfarma.com

Suomi/Finland
SanFarma Oy
Tapparakatu 166
FIN-80512 Juensuu
Puh/Tel: + 358 45657
info_dk@sanfarma.com

Sverige
SanFarma
Vaksealgatan 34
S-256 22 Uppsala
Tel: + 46 (0) 12345646
info_dk@sanfarma.com

United Kingdom
SanFarma UK
49 Walton Street
Oxford OX3 2JH UK
Tel: + 44 (0) 1856 2311
drugsafety@sanfarma.co.uk

Diese Packungsbeilage wurde zuletzt überarbeitet im November 2011.

Weitere Informationsquellen
Ausführliche Informationen zu diesem Arzneimittel sind auf den Internetseiten der Europäischen Arzneimittel-Agentur http://www.ema.europa.eu/ verfügbar. Sie finden dort auch Links zu anderen Internetseiten über seltene Erkrankungen und Behandlungen.

Diese Packungsbeilage ist auf den Internetseiten der Europäischen Arzneimittel-Agentur in allen EU-Amtssprachen verfügbar.

Appendix 5: German short text package leaflet with model template

Lesen Sie bitte aufmerksam die Packungsbeilage!

Enal 20 mg Tabletten

1. Wofür wird Enal verwendet?

- gegen hohen Blutdruck
- gegen verringerte Herzleistung
- zur Vorbeugung einer verringerten Herzleistung bei eingeschränkter Funktion der linken Herzkammer

2. Was müssen Sie vor Einnahme von Enal beachten?

Nicht einnehmen bei

- Allergie gegen einen Bestandteil von Enal oder Stoffe deren Namen auf -pril enden
- während einer früheren Behandlung mit ähnlichen Mitteln aufgetretenen, starken Gewebeschwellungen
- Neigung zu starken Schwellungen tiefer Hautschichten
- Schwangerschaft

Erst nach Arztrücksprache einnehmen bei

- Risiko für starken Blutdruckabfall, durch gestörten Salz- und Flüssigkeitshaushalt
- Ausflussbehinderung aus der linken Herzkammer
- verminderter Herz- oder Gehirndurchblutung
- eingeschränkter Nierenfunktion
- verengten Blutgefäßen der Niere
- nach Transplantation einer Niere
- Gelbsucht oder erhöhten Leberwerten
- reduzierter Anzahl weißer Blutkörperchen
- Erkrankung des Bindegewebes mit Gefäßbeteiligung
- Zuckerkrankheit
- Auftreten eines hartnäckigen, trocknen Hustens
- Risiko einer Erhöhung der Kaliumwerte
- unzureichender Blutdrucksenkung, insbesondere bei Menschen mit schwarzer Hautfarbe
- Therapie zur Abschwächung einer Allergie gegenüber Insektengiften
- Gebrauch spezieller Membranen zur Dialyse
- Entfernen von LDL-Cholesterin mit Dextransulfat
- bevorstehender Operation oder Narkose, einschließlich beim Zahnarzt
- Stillzeit
  Verwenden Sie Enal in der Stillzeit nur wenn der Arzt es für unbedingt notwendig einschätzt.

Einnahme mit anderen Arzneimitteln

Informieren Sie Ihren Arzt oder Apotheker bei gleichzeitigem oder kürzlichem Gebrauch anderer Arzneimittel. Dies betrifft insbesondere:

- harntreibende Mittel
- kaliumhaltige Mittel
- Heparin: ein gerinnungshemmendes Mittel
- andere blutdrucksenkende Mittel
- Allopurinol: ein harnsäuresenkendes Mittel
- Lithium: ein Mittel gegen Depressionen
- andere Mittel gegen Depressionen oder psychische Erkrankungen
- Procainamid: ein Mittel gegen Herzrhythmusstörungen
- Mittel zur Betäubung oder Narkose
- Mittel gegen Schmerzen, Entzündungen und Fieber, wie Acetylsalicylsäure, Ibuprofen, Diclofenac
- Mittel mit Wirkungen auf das Aktivitätssystem wie zur:
  - Steigerung des Blutdrucks und der Herzfrequenz
  - Erweiterung der Atemwege
- blutzuckersenkende Mittel und Insulin
- Mittel, die die Abwehrreaktionen unterdrücken

Nahrungsmittel und Getränke

Verzichten Sie auf Alkohol.

Verkehrstüchtigkeit und Maschinen

Bedienen Sie Fahrzeuge oder Maschinen erst nach Rücksprache mit Ihrem Arzt. Die Behandlung mit Enal kann Ihr Reaktionsvermögen beeinträchtigten.

3. Wie ist Enal einzunehmen?

Nehmen Sie Enal immer nach Anweisung Ihres Arztes ein.

Hoher Blutdruck

Startdosis: ¼ Tablette 1-mal täglich oder geringere Dosis
Übliche Tagesdosis: 1 Tablette 1-mal täglich
Maximale Tagesdosis: 1 Tablette 2-mal täglich

Verringerte Herzleistung und Vorbeugung

Als Startdosis schwächere Tabletten nutzen!
Übliche Tagesdosis: 1 Tablette 1-mal täglich
Maximale Tagesdosis: 1 Tablette 2-mal täglich

Nierenkranke und über 65-Jährige

Die Dosis ist von der Nierenfunktion abhängig.

Kinder unter 18 Jahre

Enal ist nur für Kinder zur Behandlung von Bluthochdruck vorgesehen. Jedoch sind Neugeborene und Kinder mit Nierenerkrankung generell von der Therapie auszuschließen

- 20 bis 50 kg Körpergewicht
  Als Startdosis schwächere Tabletten nutzen!
  Maximale Tagesdosis: 1 Tablette 1-mal täglich
- über 50 kg Körpergewicht
  Startdosis: ¼ Tablette 1-mal täglich
  Maximale Tagesdosis: 1 Tablette 2-mal täglich

Art der Einnahme

- sitzend oder stehend mit einem Glas Wasser mit mindestens 100 ml Inhalt
- Abstand zu Mahlzeiten ist nicht zu beachten
- Teilung der Tabletten wenn gemäß Dosis erforderlich:
  Siehe Abbildung!

Dauer der Einnahme

- bestimmt Ihr Arzt.

Bei Einnahme von zu viel Enal

Informieren Sie sofort einen Arzt.

Bei vergessener Einnahme

Nehmen Sie nicht die doppelte Dosis ein, sondern setzen Sie die Einnahme wie verordnet fort.

Abbruch der Einnahme

Nur bei Arztanweisung Therapie beenden. Absetzen oder Dosisänderung ohne Arztabsprache verringert die Wirkung oder steigert das Risiko von Folgeschäden.

4. Mögliche Nebenwirkungen

Studien belegen, dass bei korrektem Gebrauch von Enal der Nutzen überwiegt.

Häufigkeiten der Nebenwirkungen:
Sehr häufig, betrifft mehr als 1 von 10 Personen

- Verschwommensehen
- Schwindel
- Husten
- Übelkeit
- Schwächegefühl

Häufig, betrifft 1 bis 10 von 100 Personen
- meist schmerzhafte, **starke Schwellungen tiefer Hautschichten**, oft im Gesicht
  Sie benötigen sofortige ärztliche Behandlung bei Gewebeschwellungen von Kehlkopf und/oder Zunge.
- Kopfschmerzen, Depressionen
- Blutdruckabfall beim Aufrichten, Ohnmacht
- Herzinfarkt, Schlaganfall
- Schmerzen im Brustkorb, Herzengegefühl
- Herzrhythmusstörungen, erhöhter Puls
- Atemnot
- Durchfall, Bauchschmerzen, Geschmacksveränderungen
- Ausschlag
- Müdigkeit
- zu viel Kalium oder Kreatinin im Blut

Gelegentlich, betrifft 1 bis 10 von 1.000 Personen
- Mangel roter Blutkörperchen
- niedrige Blutzuckerwerte
- Verwirrtheit, Nervosität
- Schläfrigkeit, Schlaflosigkeit
- Missempfindungen
- Herzklopfen
- verstärkte Schleimabsonderung aus der Nase
- Halsschmerzen, Heiserkeit
- krampfartige Verengung der Bronchien, Asthma
- Darmverschluss
- entzündete Bauchspeicheldrüse
- Erbrechen, Verdauungsstörungen, Verstopfung
- Appetitlosigkeit, Magenreizung
- Mundtrockenheit
- Magengeschwür
- vermehrtes Schwitzen
- Juckreiz, Nesselsucht
- Haarausfall
- gestörte Nierenfunktion, Nierenversagen, Eiweiß im Urin
- Impotenz
- Muskelkrämpfe
- Gesichtsrötung, Fieber
- Unwohlsein
- Ohrgeräusche
- zu viel Harnstoff im Blut, Natriummangel im Blut

Selten, betrifft 1 bis 10 von 10.000 Personen
- Mangel bestimmter weißer Blutzellen, geschwollene Lymphknoten
  Informieren Sie sofort einen Arzt bei **Fieber, geschwollenen Lymphknoten** und/oder **Halsentzündung**, damit er das weiße Blutbild untersucht.
- **Gelbsucht, Anstieg der Leberenzyme**
  Beendigen Sie sofort die Einnahme von Enal und informieren Sie einen Arzt bei Gelbsucht oder deutlichem Anstieg der Leberenzymwerte
- verschiedene, **schwerwiegende Formen von Hautausschlag** mit Fieber und Blasenbildung
  Beenden Sie sofort die Einnahme von Enal und informieren Sie einen Arzt bei Verdacht einer schwerwiegenden Hautreaktion.
- Mangel des roten Blutfarbstoffes
- verringerte Knochenmarkfunktion
- Krankheiten der körpereigenen Abwehr
- verändertes Träumen, Schlafstörungen
- gestörte Durchblutung in Fingern und Zehen
- abnorme Anhäufung von Stoffen in der Lunge
- Schnupfen
- allergische Entzündungen der Lunge
- Entzündung der Schleimhaut von Mund oder Zunge
- Leberversagen, Leberentzündung.
- Lichtempfindlichkeit oder andere Hautreaktionen
- reduzierte Harnausscheidung
- vergrößerte Brustdrüse bei Männern

Sehr selten, betrifft weniger als 1 von 10.000 Personen
- Gewebeschwellung des Darms

Informieren Sie bei Nebenwirkungen immer den Arzt oder Apotheker.

5. Wie ist Enal aufzubewahren?
- für Kinder unzugänglich
- nicht anwenden nach dem Verfalldatum auf dem Etikett oder des Behältnisses
- nicht über 25°C aufbewahren

Enal ist nur für Sie verordnet. Geben Sie es nicht anderen Menschen, auch wenn diese ähnliche Beschwerden haben.

6. Weitere Information
Zusammensetzung
Eine Tablette enthält:
- wirksamer Bestandteil:
  20 mg Enalaprilmaleat
- weitere Bestandteile:
  Croscarmellose-Natrium, Eisen(III)-oxid, Eisenoxidhydrat, Lactose-Monohydrat, Magnesiumstearat, Natriumhydrogencarbonat, vorverkleisterte Maisstärke.

Hersteller
SanFarma
Sonnenstraße 1
D-12345 Sonne
Tel: 0423/233345
Fax: 0423/23344
Sanfarma@info.de

Letzte Überarbeitung der Packungsbeilage
11/2011

Appendix 6: German short text package leaflet with QRD template 7.3.1

GEBRAUCHSINFORMATION: INFORMATION FÜR DEN ANWENDER

Enal 20 mg Tabletten

Enalaprilmaleat

Lesen Sie die gesamte Packungsbeilage sorgfältig durch, bevor Sie mit der Einnahme dieses Arzneimittels beginnen.
- Heben Sie die Packungsbeilage auf. Vielleicht möchten Sie diese später nochmals lesen.
- Wenn Sie weitere Fragen haben, wenden Sie sich an Ihren Arzt oder Apotheker.
- Dieses Arzneimittel wurde Ihnen persönlich verschrieben. Geben Sie es nicht an Dritte weiter. Es kann anderen Menschen schaden, auch wenn diese die gleichen Beschwerden haben wie Sie.
- Wenn eine der aufgeführten Nebenwirkungen Sie erheblich beeinträchtigt oder Sie Nebenwirkungen bemerken, die nicht in dieser Gebrauchsinformation angegeben sind, informieren Sie bitte Ihren Arzt oder Apotheker.

Diese Packungsbeilage beinhaltet:

1. WAS IST ENAL UND WOFÜR WIRD ES ANGEWENDET?

Enal ist ein ACE-Hemmer, d. h. ein Arzneimittel mit blutdrucksenkenden und herzentlastenden Eigenschaften.

Enal wird angewendet:
- gegen hohen Blutdruck
- gegen verringerte Herzleistung
- zur Vorbeugung einer verringerten Herzleistung bei eingeschränkter Funktion der linken Herzkammer

2. WAS MÜSSEN SIE VOR DER EINNAHME VON ENAL BEACHTEN?

Enal darf nicht eingenommen werden,
- wenn Sie überempfindlich (allergisch) gegen Enalapril, Stoffe deren Namen auf -pril enden oder einen der sonstigen Bestandteile von Enal sind.
- wenn bei Ihnen während einer früheren Behandlung mit ähnlichen Mitteln starke Gewebeschwellungen auftraten
- wenn Sie eine Neigung zu starken Schwellungen tiefer Hautschichten haben
- während der Schwangerschaft

Besondere Vorsicht bei der Einnahme von Enal ist erforderlich,
- wenn bei Ihnen das Risiko für einen starken Blutdruckabfall durch gestörten Salz- und Flüssigkeitshaushalt besteht
- wenn Sie eine Ausflussbehinderung aus der linken Herzkammer haben
- wenn Sie an einer verminderten Herz- oder Gehirndurchblutung leiden
- wenn Ihre Nierenfunktion eingeschränkt ist
- wenn Sie verengte Blutgefäße der Niere haben
- nach Transplantation einer Niere
- wenn Sie Gelbsucht oder erhöhte Leberwerte haben
- wenn Sie eine reduzierte Anzahl weißer Blutkörperchen haben
- wenn Sie an einer Erkrankung des Bindegewebes mit Gefäßbeteiligung leiden
- wenn Sie unter Zuckerkrankheit leiden
- wenn ein hartnäckiger, trockner Husten auftritt
- wenn bei Ihnen das Risiko einer Erhöhung der Kaliumwerte besteht
- wenn Sie eine unzureichende Blutdrucksenkung haben, insbesondere bei Menschen mit schwarzer Hautfarbe
- wenn Sie eine Therapie zur Abschwächung einer Allergie gegenüber Insektengiften erhalten
- wenn Sie spezielle Membranen zur Dialyse gebrauchen
- wenn bei Ihnen LDL-Cholesterin mit Dextransulfat entfernt wird
- wenn Sie vor einer Operation oder Narkose, einschließlich beim Zahnarzt stehen
- während der Stillzeit:
  Verwenden Sie Enal in der Stillzeit nur wenn der Arzt es für unbedingt notwendig einschätzt.

Bei Einnahme von Enal mit anderen Arzneimitteln
Bitte informieren Sie Ihren Arzt oder Apotheker, wenn Sie andere Arzneimittel einnehmen bzw. vor kurzem eingenommen haben, auch wenn es sich um nicht verschreibungspflichtige Arzneimittel handelt. Dies betrifft insbesondere:
- harntreibende Mittel
- kaliumhaltige Mittel
- Heparin: ein gerinnungshemmendes Mittel
- andere blutdrucksenkende Mittel
- Allopurinol: ein harnsäuresenkendes Mittel
- Lithium: ein Mittel gegen Depressionen
- andere Mittel gegen Depressionen oder psychische Erkrankungen
- Procainamid: ein Mittel gegen Herzrhythmusstörungen
- Mittel zur Betäubung oder Narkose
- Mittel gegen Schmerzen, Entzündungen und Fieber, wie Acetylsalicylsäure, Ibuprofen, Diclofenac
- Mittel mit Wirkungen auf das Aktivitätssystem wie zur:
  – Steigerung des Blutdrucks und der Herzfrequenz
  – Erweiterung der Atemwege
- blutzuckersenkende Mittel und Insulin
- Mittel, die die Abwehrreaktionen unterdrücken

Bei Einnahme von Enal zusammen mit Nahrungsmitteln und Getränken
Verzichten Sie auf Alkohol.

Schwangerschaft und Stillzeit
Fragen Sie vor der Einnahme von allen Arzneimitteln Ihren Arzt oder Apotheker um Rat.
Schwangerschaft:
Sie sollten Enal in der Schwangerschaft nicht einnehmen.
Stillzeit:
Verwenden Sie Enal in der Stillzeit nur wenn der Arzt es für unbedingt notwendig einschätzt.

Verkehrstüchtigkeit und das Bedienen von Maschinen
Bedienen Sie Fahrzeuge oder Maschinen erst nach Rücksprache mit Ihrem Arzt. Die Behandlung mit Enal kann Ihr Reaktionsvermögen beeinträchtigten.

Wichtige Informationen über bestimmte sonstige Bestandteile von Enal
Dieses Arzneimittel enthält Lactose. Bitte nehmen Sie es daher erst nach Rücksprache mit dem Arzt ein, wenn Ihnen bekannt ist, dass Sie unter einer Unverträglichkeit gegenüber bestimmten Zuckern leiden.

3. WIE IST ENAL EINZUNEHMEN?

Nehmen Sie Enal immer genau nach Anweisung des Arztes ein. Bitte fragen Sie bei Ihrem Arzt oder Apotheker nach, wenn Sie sich nicht ganz sicher sind. Falls vom Arzt nicht anders verordnet, ist die übliche Dosis:

Hoher Blutdruck
Startdosis: ¼ Tablette 1-mal täglich oder geringere Dosis
Übliche Tagesdosis: 1 Tablette 1-mal täglich
Maximale Tagesdosis: 1 Tablette 2-mal täglich

Verringerte Herzleistung und Vorbeugung
Als Startdosis schwächere Tabletten nutzen!
Übliche Tagesdosis: 1 Tablette 1-mal täglich
Maximale Tagesdosis: 1 Tablette 2-mal täglich

Nierenkranke und über 65-Jährige
Die Dosis ist von der Nierenfunktion abhängig.

Anwendung bei Kindern und Jugendlichen
Enal ist nur für Kinder zur Behandlung von Bluthochdruck vorgesehen. Jedoch sind Neugeborene und Kinder mit Nierenerkrankung generell von der Therapie auszuschließen
- 20 bis 50 kg Körpergewicht
  Als Startdosis schwächere Tabletten nutzen!
  Maximale Tagesdosis: 1 Tablette 1-mal täglich
- über 50 kg Körpergewicht
  Startdosis: ¼ Tablette 1-mal täglich
  Maximale Tagesdosis: 1 Tablette 2-mal täglich

Art der Einnahme
- sitzend oder stehend mit einem Glas Wasser mit mindestens 100 ml Inhalt
- Abstand zu Mahlzeiten ist nicht zu beachten
- Teilung der Tabletten wenn gemäß Dosis erforderlich: Siehe Abbildung!

Dauer der Einnahme
- bestimmt Ihr Arzt.

Wenn Sie eine größere Menge von Enal eingenommen haben, als Sie sollten
Informieren Sie sofort einen Arzt.

Wenn Sie die Einnahme von Enal vergessen haben
Nehmen Sie nicht die doppelte Dosis ein, sondern setzen Sie die Einnahme wie verordnet fort.

Wenn Sie die Einnahme von Enal abbrechen
Nur bei Arztanweisung Therapie beenden. Absetzen oder Dosisänderung ohne Arztabsprache verringert die Wirkung oder steigert das Risiko von Folgeschäden.

Wenn Sie weitere Fragen zur Anwendung des Arzneimittels haben, fragen Sie Ihren Arzt oder Apotheker.

4. WELCHE NEBENWIRKUNGEN SIND MÖGLICH?

Wie alle Arzneimittel kann Enal Nebenwirkungen haben, die aber nicht bei jedem auftreten müssen.

Bei der Bewertung von Nebenwirkungen werden folgende Häufigkeitsangaben zugrunde gelegt:

Sehr häufig	mehr als 1 von 10 Behandelten
Häufig	weniger als 1 von 10, aber mehr als 1 von 100 Behandelten
Gelegentlich	weniger als 1 von 100, aber mehr als 1 von 1000 Behandelten
Selten	weniger als 1 von 1000, aber mehr als 1 von 10.000 Behandelten
Sehr selten	weniger als 1 von 10.000 Behandelten, oder unbekannt

Sehr häufige Nebenwirkungen
- Verschwommensehen
- Schwindel
- Husten
- Übelkeit
- Schwächegefühl

Häufige Nebenwirkungen
- Kopfschmerzen, Depressionen
- Blutdruckabfall beim Aufrichten, Ohnmacht
- Herzinfarkt, Schlaganfall
- Schmerzen im Brustkorb, Herzengegefühl
- Herzrhythmusstörungen, erhöhter Puls
- Atemnot
- Durchfall, Bauchschmerzen, Geschmacksveränderungen
- Ausschlag
- Müdigkeit
- meist schmerzhafte, starke Schwellungen tiefer Hautschichten, oft im Gesicht
- zu viel Kalium oder Kreatinin im Blut

Gelegentliche Nebenwirkungen
- Mangel roter Blutkörperchen
- niedrige Blutzuckerwerte
- Verwirrtheit, Nervosität
- Schläfrigkeit, Schlaflosigkeit
- Missempfindungen
- Herzklopfen
- verstärkte Schleimabsonderung aus der Nase
- Halsschmerzen, Heiserkeit
- krampfartige Verengung der Bronchien, Asthma
- Darmverschluss
- entzündete Bauchspeicheldrüse
- Erbrechen, Verdauungsstörungen, Verstopfung
- Appetitlosigkeit, Magenreizung
- Mundtrockenheit
- Magengeschwür
- vermehrtes Schwitzen
- Juckreiz, Nesselsucht
- Haarausfall
- gestörte Nierenfunktion, Nierenversagen, Eiweiß im Urin
- Impotenz
- Muskelkrämpfe
- Gesichtsrötung, Fieber
- Unwohlsein
- Ohrgeräusche
- zu viel Harnstoff im Blut, Natriummangel im Blut

Seltene Nebenwirkungen
- Mangel bestimmter weißer Blutzellen, geschwollene Lymphknoten
- Mangel des roten Blutfarbstoffes
- verringerte Knochenmarkfunktion
- Krankheiten der körpereigenen Abwehr
- verändertes Träumen, Schlafstörungen
- gestörte Durchblutung in Fingern und Zehen
- abnorme Anhäufung von Stoffen in der Lunge
- Schnupfen
- allergische Entzündungen der Lunge
- Entzündung der Schleimhaut von Mund oder Zunge
- Leberversagen, Leberentzündung, Gelbsucht, Anstieg der Leberenzyme
- verschiedene, schwerwiegende Formen von Hautausschlag mit Fieber und Blasenbildung
- Lichtempfindlichkeit oder andere Hautreaktionen
- reduzierte Harnausscheidung
- vergrößerte Brustdrüse bei Männern

Sehr seltene Nebenwirkungen
- Gewebeschwellung des Darms

Gegenmaßnahmen
Beendigen Sie sofort die Einnahme von Enal und informieren Sie einen Arzt bei Verdacht einer schwerwiegenden Hautreaktion.
Sie benötigen sofortige ärztliche Behandlung bei Gewebeschwellungen von Kehlkopf und/oder Zunge.
Beenden Sie sofort die Einnahme von Enal und informieren Sie einen Arzt bei Gelbsucht oder deutlichem Anstieg der Leberenzymwerte.
Informieren Sie sofort einen Arzt bei Fieber, geschwollenen Lymphknoten und/oder Halsentzündung, damit er das weiße Blutbild untersucht.

Informieren Sie bitte Ihren Arzt oder Apotheker, wenn eine der aufgeführten Nebenwirkungen Sie erheblich beeinträchtigt oder Sie Nebenwirkungen bemerken, die nicht in dieser Gebrauchsinformation angegeben sind.

5. WIE IST ENAL AUFZUBEWAHREN?
Arzneimittel für Kinder unzugänglich aufbewahren!
Sie dürfen das Arzneimittel nach dem auf dem Etikett oder dem Behältnis nach EXP angegebenen Verfalldatum nicht mehr anwenden. Das Verfalldatum bezieht sich auf den letzten Tag des Monats.
Nicht über 25°C aufbewahren.
Das Arzneimittel darf nicht im Abwasser oder Haushaltsabfall entsorgt werden. Fragen Sie Ihren Apotheker wie das Arzneimittel zu entsorgen ist, wenn Sie es nicht mehr benötigen. Diese Maßnahme hilft die Umwelt zu schützen.

6. WEITERE INFORMATIONEN
Was Enal enthält
- Der Wirkstoff ist: Enalaprilmaleat.
  Eine Tablette enthält 20 mg Enalaprilmaleat.
- Die sonstigen Bestandteile sind: Croscarmellose-Natrium, Eisen(III)-oxid, Eisenoxidhydrat, Lactose-Monohydrat, Magnesiumstearat, Natriumhydrogencarbonat, vorverkleisterte Maisstärke.

Wie Enal aussieht und Inhalt der Packung:
Runde, gelbliche Tabletten; Packungen mit 30, 50 und 100 Tabletten.

Pharmazeutischer Unternehmer und Hersteller
SanFarma
Sonnenstraße 1
D-12345 Sonne
Tel: 0423/233345
Fax: 0423/23344
Sanfarma@info.de

Falls weitere Informationen über das Arzneimittel gewünscht werden, setzen Sie sich bitte mit dem örtlichen Vertreter des Pharmazeutischen Unternehmers in Verbindung.

België/Belgique/Belgien
SanFarma S.A
Rue de La Monnaie 24
B-1500 Bruxelles
Tél/Tel: + 32 (0) 800 56 456
SFBelgium_info@sanfarma.com

България
ЗАНФАРМА
Bul. Todor Slivnista Г
ЗВГИ София
Тел.: + 359 4567656
info-sf@sanfarma.com

Česká republika
SanFarma Pharmaceuticals CR
Moskevská 7
CZ Praha
Tel: +420 255366
sfarma_cr@sanfarma.com

Danmark
SanFarma Denmark A/S
Tarp Hovedvej 12
DK-5277 Esbjerg
Tlf: + 45 567893
info_dk@sanfarma.com

Deutschland
SanFarma
Sonnenstraße 1
D-12345 Sonne
Tel: + 49 (0) 423/233345
Sanfarma@info.de

Eesti
SanFarma Baltics Eesti Filiaal
Telliskivi plats 3
EE – 10564 Kesklinn
Tel: +372 567523
Sanfarmaeesti@sanfarma.com

Ελλάδα
SanFarma Ελλάς
Αλεάνδ□ου
GR-457 77 Παλαμάς
Τηλ: + 30 5669 222
info@sanfarma.gr

España
SanFarma S.L.U.
Calle de los Riato 12
E-75421 Montilla del Palancar
Tel: + 34 5669 111
info@sanfarma.es

France
SanFarma France
Rue de la Loire 34
F-24985 Tours
Tél: + 33 (0) 25 665544
contact@sanfarma-france.com

Ireland
SanFarma Ireland
89 Dromore Street
IRL - Banbridge BT34 5JH
Tel: + 353 (0) 5662333
info_ireland@sanfarma.com

Ísland
SanFarma
Tjarnagata 78
IS-105 Reykjavík
Sími: + 354 5622366
isregulatory@sanfarma.com

Italia
SanFarma Italy S.p.A.
Via Tuscolana 33
I-54896 Roma
Tel: + 39 (0) 3562 112
info@s-farma.com

Κύπρος
SanFarma Ελλάς
Σπύρολλ
CY-000 00 Γερίου
Τηλ: + 30 45433 11
cyprus_info@sanfarma.com

Latvija
SanFarma Latvijā
Liela Iela 44
Jelgava, LV-1256
Tel: + 371 453 222
Info_lv@sanfarma.com

Lietuva
SanFarma Baltics
Perkūno alėja 44
LT 44301 Kaunas
Tel: +370 564 232
info_lietuva@sanfarma.com

Luxembourg/Luxemburg
SanFarma S.A.
Route d'Eich 66
L-1510 Luxembourg
Tél/Tel: + 32 (0) 800 56 456
SFBelgium_info@sanfarma.com

Magyarország
SanFarma Magyarország Zrt
Attila hid 8
H-5688 Budapest
Tel.: + 36 569 599
service.hungary@sanfarma.com

Malta
SanFarma Ελλάς
Triq Il-Konti 666
MT-4596 San Qormi
Tel: + 356 234588
info_malta@sfarma.com

Nederland
SanFarma Nederland B.V.
De la Meppelweg 25
NL-5663 AA Den Haag
Tel: + 31 (0) 453 1189
info.sanfarma-nl@sanfarma.com

Norge
SanFarma Norway A.S.
Grünerløkka 3
N-9548 Oslo
Tlf: + 47 254 923
info.sanfarma@sanfarma.com

Österreich
SanFarma Generics
Nußdorfer Straße 33
A-2156 Wien
Tel: + 43 (0) 456 11888
Sanfarma@info.de

Polska
SanFarma Polska Sp.
Wyszogrodzka 2
PL – 77 455 Plock
Tel.: + 48 55 69971
sanfarmapolska@sanfarma.com

Portugal
SanFarma Farmacéuticos
São Domingo de Pedreira 578
P-4958-257 Odivelas
Tel: + 351 5956 223
informacao@sanfarma.com

România
SanFarma Pharmaceuticals
Strada Lungă 44
Sibiu 560220 – RO
Tel: + 40 200 551
sanfarmaromania@sanfarma.com

Slovenija
SanFarma d.d.
Trešnjevka-sjever 3
SI-1000 Zagreb
Tel: + 386 5623 66
sanfarma_slovenia@sanfarma.com

Slovenská republika
SanFarma Slovakia
Hlavná 2566/11
SK-070 02 Prešov
Tel: + 421 45213665
sanfarma_sk@sanfarma.com

Suomi/Finland
SanFarma Oy
Tapparakatu 166
FIN-80512 Juensuu
Puh/Tel: + 358 45657
info_dk@sanfarma.com

Sverige
SanFarma
Vaksealgatan 34
S-256 22 Uppsala
Tel: + 46 (0) 12345646
info_dk@sanfarma.com

United Kingdom
SanFarma UK
49 Walton Street
Oxford OX3 2JH UK
Tel: + 44 (0) 1856 2311
drugsafety@sanfarma.co.uk

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Ausführliche Informationen zu diesem Arzneimittel sind auf der Website der Europäischen Arzneimittel-Agentur http://www.ema.europa.eu/ verfügbar. Es gibt auch Links zu anderen Websites über seltene Erkrankungen und Behandlungen.

Appendix 7: German short text package leaflet with QRD template 8

Gebrauchsinformation: Information für Patienten

Enal 20 mg Tabletten

Enalaprilmaleat

Lesen Sie die gesamte Packungsbeilage sorgfältig durch, bevor Sie mit der Einnahme dieses Arzneimittels beginnen, denn sie enthält wichtige Informationen.
- Heben Sie die Packungsbeilage auf. Vielleicht möchten Sie diese später nochmals lesen.
- Wenn Sie weitere Fragen haben, wenden Sie sich an Ihren Arzt, Apotheker oder Ihre Pflegekraft.
- Dieses Arzneimittel wurde Ihnen persönlich verschrieben. Geben Sie es nicht an Dritte weiter. Es kann anderen Menschen schaden, auch wenn diese die gleichen Beschwerden haben wie Sie.
- Wenn Sie Nebenwirkungen bemerken, wenden Sie sich an Ihren Arzt, Apotheker oder Ihre Pflegefachkraft. Dies gilt auch für Nebenwirkungen, die nicht in dieser Packungsbeilage angegeben sind.

Was in dieser Packungsbeilage steht

1. Was ist Enal und wofür wird es angewendet?

Enal enthält Enalapril. Es ist ein ACE-Hemmer, d.h. ein Arzneimittel mit blutdrucksenkenden und herzentlastenden Eigenschaften.

Enal wird angewendet:
- gegen hohen Blutdruck
- gegen verringerte Herzleistung
- zur Vorbeugung einer verringerten Herzleistung bei eingeschränkter Funktion der linken Herzkammer

Dieses Arzneimittel bewirkt eine Blutdrucksenkung, was hilftreich zur Vorbeugung von Komplikationen durch erhöhten Blutdruck ist.

2. Was sollten Sie vor der Einnahme von Enal beachten?

Enal darf nicht eingenommen werden,
- wenn Sie allergisch gegen Enalapri, Stoffe deren Namen auf -pril enden oder einen der im Abschnitt 6. genannten sonstigen Bestandteile sind
- wenn bei Ihnen während einer früheren Behandlung mit ähnlichen Mitteln starke Gewebeschwellungen auftraten
- bei Neigung zu starken Schwellungen tiefer Hautschichten
- während der Schwangerschaft

Warnhinweise und Vorsichtsmaßnahmen
Bitte sprechen Sie mit Ihrem Arzt, Apotheker oder Ihrer Pflegefachkraft, bevor Sie Enal einnehmen, bei:
- Risiko für starken Blutdruckabfall, durch gestörten Salz- und Flüssigkeitshaushalt
- Ausflussbehinderung aus der linken Herzkammer
- verminderter Herz- oder Gehirndurchblutung
- eingeschränkter Nierenfunktion
- verengten Blutgefäßen der Niere
- nach Transplantation einer Niere
- Gelbsucht oder erhöhten Leberwerten
- reduzierter Anzahl weißer Blutkörperchen
- Erkrankung des Bindegewebes mit Gefäßbeteiligung
- Zuckerkrankheit
- Auftreten eines hartnäckigen, trocknen Hustens
- Risiko einer Erhöhung der Kaliumwerte
- unzureichender Blutdrucksenkung, insbesondere bei Menschen mit schwarzer Hautfarbe
- Therapie zur Abschwächung einer Allergie gegenüber Insektengiften
- Gebrauch spezieller Membranen zur Dialyse
- Entfernen von LDL-Cholesterin mit Dextransulfat
- bevorstehender Operation oder Narkose, einschließlich beim Zahnarzt
- Stillzeit:
  Verwenden Sie Enal in der Stillzeit nur wenn der Arzt es für unbedingt notwendig einschätzt.

Kinder und Jugendliche
Enal ist nur für Kinder zur Behandlung von Bluthochdruck vorgesehen. Jedoch sind Neugeborene und Kinder mit Nierenerkrankung generell von der Therapie auszuschließen

Einnahme von Enal zusammen mit anderen Arzneimitteln
Informieren Sie Ihren Arzt oder Apotheker wenn Sie andere Arzneimittel einnehmen, kürzlich andere Arzneimittel eingenommen haben oder beabsichtigen andere Arzneimittel einzunehmen. Dies betrifft insbesondere:
- harntreibende Mittel
- kaliumhaltige Mittel
- Heparin (ein gerinnungshemmendes Mittel)
- andere blutdrucksenkende Mittel
- Allopurinol (ein harnsäuresenkendes Mittel)
- Lithium (ein Mittel gegen Depressionen)
- andere Mittel gegen Depressionen oder psychische Erkrankungen
- Procainamid (ein Mittel gegen Herzrhythmusstörungen)
- Mittel zur Betäubung oder Narkose
- Mittel gegen Schmerzen, Entzündungen und Fieber, wie Acetylsalicylsäure, Ibuprofen, Diclofenac
- Mittel mit Wirkungen auf das Aktivitätssystem wie zur:
  - Steigerung des Blutdrucks und der Herzfrequenz
  - Erweiterung der Atemwege
- blutzuckersenkende Mittel und Insulin
- Mittel, die die Abwehrreaktionen unterdrücken

Einnahme von Enal zusammen mit Nahrungsmitteln, Getränken und Alkohol
Verzichten Sie auf Alkohol.

Schwangerschaft, Stillzeit und Zeugungs-/Gebärfähigkeit
Wenn Sie schwanger sind oder stillen, oder wenn Sie vermuten, schwanger zu sein oder beabsichtigen, schwanger zu werden, fragen Sie vor der Einnahme dieses Arzneimittels Ihren Arzt oder Apotheker um Rat.
Schwangerschaft:
Sie sollten Enal in der Schwangerschaft nicht einnehmen.
Stillzeit:
Verwenden Sie Enal in der Stillzeit nur wenn der Arzt es für unbedingt notwendig einschätzt.

Verkehrstüchtigkeit und Fähigkeit zum Bedienen von Maschinen
Bedienen Sie Fahrzeuge oder Maschinen erst nach Rücksprache mit Ihrem Arzt. Die Behandlung mit Enal kann Ihr Reaktionsvermögen beeinträchtigten.

Enal enthält Lactose
Bitte nehmen Sie es daher erst nach Rücksprache mit dem Arzt ein, wenn Ihnen bekannt ist, dass Sie unter einer Unverträglichkeit gegenüber bestimmten Zuckern leiden.

3. Wie ist Enal einzunehmen?

Nehmen Sie dieses Arzneimittel immer genau nach Absprache mit Ihrem Arzt oder Apotheker ein. Fragen Sie bei Ihrem Arzt oder Apotheker nach, wenn Sie sich nicht sicher sind.
Die empfohlene Dosis beträgt:

Hoher Blutdruck
Startdosis: ¼ Tablette 1-mal täglich oder geringere Dosis
Übliche Tagesdosis: 1 Tablette 1-mal täglich
Maximale Tagesdosis: 1 Tablette 2-mal täglich

Verringerte Herzleistung und Vorbeugung
Als Startdosis schwächere Tabletten nutzen!
Übliche Tagesdosis: 1 Tablette 1-mal täglich
Maximale Tagesdosis: 1 Tablette 2-mal täglich

Nierenkranke und über 65-Jährige
Die Dosis ist von der Nierenfunktion abhängig.

Anwendung bei Kindern und Jugendlichen
Enal ist nur für Kinder zur Behandlung von Bluthochdruck vorgesehen. Jedoch sind Neugeborene und Kinder mit Nierenerkrankung generell von der Therapie auszuschließen
- 20 bis 50 kg Körpergewicht
  Als Startdosis schwächere Tabletten nutzen!
  Maximale Tagesdosis: 1 Tablette 1-mal täglich
- über 50 kg Körpergewicht
  Startdosis: ¼ Tablette 1-mal täglich
  Maximale Tagesdosis: 1 Tablette 2-mal täglich

Art der Einnahme
- sitzend oder stehend mit einem Glas Wasser mit mindestens 100 ml Inhalt
- Abstand zu Mahlzeiten ist nicht zu beachten
- Die Tablette kann in gleiche Dosen geteilt werden.
- Teilung der Tabletten wenn gemäß Dosis erforderlich: Siehe Abbildung!

Dauer der Einnahme
- bestimmt Ihr Arzt.

Wenn Sie eine größere Menge von Enal eingenommen haben, als Sie sollten
Informieren Sie sofort einen Arzt.

Wenn Sie die Einnahme von Enal vergessen haben
Nehmen Sie nicht die doppelte Menge ein, wenn Sie die vorherige Einnahme vergessen haben.

Wenn Sie die Einnahme von Enal abbrechen
Nur bei Arztanweisung Therapie beenden. Absetzen oder Dosisänderung ohne Arztabsprache verringert die Wirkung oder steigert das Risiko von Folgeschäden.

Wenn Sie weitere Fragen zur Einnahme dieses Arzneimittels haben, wenden Sie sich an Ihren Arzt, Apotheker oder Ihre Pflegefachkraft.

4. Welche Nebenwirkungen sind möglich?

Wie alle Arzneimittel kann auch dieses Arzneimittel Nebenwirkungen haben, die aber nicht bei jedem auftreten müssen.

Häufig: kann bis zu 1 von 10 Personen betreffen
- meist schmerzhafte, starke Schwellungen tiefer Hautschichten, oft im Gesicht
  Sie benötigen sofortige ärztliche Behandlung bei Gewebeschwellungen von Kehlkopf und/oder Zunge.

Selten: kann bis zu 1 von 1.000 Personen betreffen
- Mangel bestimmter weißer Blutzellen, geschwollene Lymphknoten
  Informieren Sie sofort einen Arzt bei Fieber, geschwollenen Lymphknoten und/oder Halsentzündung, damit er das weiße Blutbild untersucht.
- Gelbsucht, Anstieg der Leberenzyme
  Beendigen Sie sofort die Einnahme von Enal und informieren Sie einen Arzt bei Gelbsucht oder deutlichem Anstieg der Leberenzymwerte.
- verschiedene, schwerwiegende Formen von Hautausschlag mit Fieber und Blasenbildung
  Beenden Sie sofort die Einnahme von Enal und informieren Sie einen Arzt bei Verdacht einer schwerwiegenden Hautreaktion.

Weitere Nebenwirkungen:
Sehr häufig: kann mehr als 1 von 10 Personen betreffen:
- Verschwommensehen
- Schwindel
- Husten
- Übelkeit
- Schwächegefühl

Häufig: kann bis zu 1 von 10 Personen betreffen
- Kopfschmerzen, Depressionen
- Blutdruckabfall beim Aufrichten, Ohnmacht
- Herzinfarkt, Schlaganfall
- Schmerzen im Brustkorb, Herzengegefühl
- Herzrhythmusstörungen, erhöhter Puls
- Atemnot
- Durchfall, Bauchschmerzen, Geschmacksveränderungen
- Ausschlag
- Müdigkeit
- zu viel Kalium oder Kreatinin im Blut

Gelegentlich: kann bis zu 1 von 100 Personen betreffen
- Mangel roter Blutkörperchen
- niedrige Blutzuckerwerte
- Verwirrtheit, Nervosität
- Schläfrigkeit, Schlaflosigkeit
- Missempfindungen
- Herzklopfen
- verstärkte Schleimabsonderung aus der Nase
- Halsschmerzen, Heiserkeit
- krampfartige Verengung der Bronchien, Asthma
- Darmverschluss
- entzündete Bauchspeicheldrüse
- Erbrechen, Verdauungsstörungen, Verstopfung
- Appetitlosigkeit, Magenreizung
- Mundtrockenheit
- Magengeschwür
- vermehrtes Schwitzen
- Juckreiz, Nesselsucht
- Haarausfall
- gestörte Nierenfunktion, Nierenversagen, Eiweiß im Urin
- Impotenz
- Muskelkrämpfe
- Gesichtsrötung, Fieber
- Unwohlsein
- Ohrgeräusche
- zu viel Harnstoff im Blut, Natriummangel im Blut

Selten: kann bis zu 1 von 1.000 Personen betreffen
- Mangel des roten Blutfarbstoffes
- verringerte Knochenmarkfunktion
- Krankheiten der körpereigenen Abwehr
- verändertes Träumen, Schlafstörungen
- gestörte Durchblutung in Fingern und Zehen
- abnorme Anhäufung von Stoffen in der Lunge
- Schnupfen
- allergische Entzündungen der Lunge
- Entzündung der Schleimhaut von Mund oder Zunge
- Leberversagen, Leberentzündung
- reduzierte Harnausscheidung
- vergrößerte Brustdrüse bei Männern

Sehr selten: kann bis zu 1 von 10.000 Personen betreffen
- Gewebeschwellung des Darms

Wenn Sie Nebenwirkungen bemerken, wenden Sie sich an Ihren Arzt, Apotheker oder Ihre Pflegefachkraft. Dies gilt auch für Nebenwirkungen, die nicht in dieser Packungsbeilage angegeben sind.

5. Wie ist Enal aufzubewahren?

Bewahren Sie dieses Arzneimittel für Kinder unzugänglich auf.
Sie dürfen das Arzneimittel nach dem auf dem Etikett oder dem Behältnis nach EXP angegebenen Verfalldatum nicht mehr anwenden. Das Verfalldatum bezieht sich auf den letzten Tag des angegebenen Monats.
Nicht über 25°C aufbewahren.
Entsorgen Sie Arzneimittel nicht im Abwasser oder Haushaltsabfall. Fragen Sie Ihren Apotheker, wie das Arzneimittel zu entsorgen ist, wenn Sie es nicht mehr verwenden. Sie tragen damit zum Schutz der Umwelt bei.

6. Inhalt der Packung und weitere Informationen

Was Enal enthält
- Der Wirkstoff ist: Enalaprilmaleat.
  Eine Tablette enthält 20 mg Enalaprilmaleat.
- Die sonstigen Bestandteile sind: Croscarmellose-Natrium, Eisen(III)-oxid, Eisenoxidhydrat, Lactose-Monohydrat, Magnesiumstearat, Natriumhydrogencarbonat, vorverkleisterte Maisstärke.

Wie Enal aussieht und Inhalt der Packung
Runde, gelbliche Tabletten; Packungen mit 30, 50 und 100 Tabletten.

Pharmazeutischer Unternehmer und Hersteller
SanFarma
Sonnenstraße 1
D-12345 Sonne
Tel: 0423/233345
Fax: 0423/23344
Sanfarma@info.de

Falls Sie weitere Informationen über das Arzneimittel wünschen, setzen Sie sich bitte mit dem örtlichen Vertreter des pharmazeutischen Unternehmers in Verbindung.

België/Belgique/Belgien
SanFarma S.A
Rue de La Monnaie 24
B-1500 Bruxelles
Tél/Tel: + 32 (0) 800 56 456
SFBelgium_info@sanfarma.com

България
ЗАНФАРМА
Bul. Todor Slivnista Г
ЗВГИ СоФия
Тел.: + 359 4567656
info-sf@sanfarma.com

Česká republika
SanFarma Pharmaceuticals CR
Moskevská 7
CZ Praha
Tel: +420 255366
sfarma_cr@sanfarma.com

Danmark
SanFarma Denmark A/S
Tarp Hovedvej 12
DK-5277 Esbjerg
Tlf: + 45 567893
info_dk@sanfarma.com

Deutschland
SanFarma
Sonnenstraße 1
D-12345 Sonne
Tel: + 49 (0) 423/233345
Sanfarma@info.de

Eesti
SanFarma Baltics Eesti Filiaal
Telliskivi plats 3
EE – 10564 Kesklinn
Tel: +372 567523
Sanfarmaeesti@sanfarma.com

Ελλάδα
SanFarma Ελλάς
Αλεάνδ□ου
GR-457 77 Παλαμάς
Τηλ: + 30 5669 222
info@sanfarma.gr

España
SanFarma S.L.U.
Calle de los Riato 12
E-75421 Montilla del Palancar
Tel: + 34 5669 111
info@sanfarma.es

France
SanFarma France
Rue de la Loire 34
F-24985 Tours
Tél: + 33 (0) 25 665544
contact@sanfarma-france.com

Ireland
SanFarma Ireland
89 Dromore Street
IRL - Banbridge BT34 5JH
Tel: + 353 (0) 5662333
info_ireland@sanfarma.com

Ísland
SanFarma
Tjarnagata 78
IS-105 Reykjavík
Sími: + 354 5622366
isregulatory@sanfarma.com

Italia
SanFarma Italy S.p.A.
Via Tuscolana 33
I-54896 Roma
Tel: + 39 (0) 3562 112
info@s-farma.com

Κύπρος
SanFarma Ελλάς
Σπύρολλ
CY-000 00 Γαρίου
Τηλ: + 30 45433 11
cyprus_info@sanfarma.com

Latvija
SanFarma Latvijā
Liela lela 44
Jelgava, LV-1256
Tel: + 371 453 222
Info_lv@sanfarma.com

Lietuva
SanFarma Baltics
Perkūno alėja 44
LT 44301 Kaunas
Tel: +370 564 232
info_lietuva@sanfarma.com

Luxembourg/Luxemburg
SanFarma S.A.
Route d'Eich 66
L-1510 Luxembourg
Tél/Tel: + 32 (0) 800 56 456
SFBelgium_info@sanfarma.com

Magyarország
SanFarma Magyarország Zrt
Attila hid 8
H-5688 Budapest
Tel.: + 36 569 599
service.hungary@sanfarma.com

Malta
SanFarma Ελλάς
Triq Il-Konti 666
MT-4596 San Qormi
Tel: + 356 234588
info_malta@sfarma.com

Nederland
SanFarma Nederland B.V.
De la Meppelweg 25
NL-5663 AA Den Haag
Tel: + 31 (0) 453 1189
info.sanfarma-nl@sanfarma.com

Norge
SanFarma Norway A.S.
Grünerløkka 3
N-9548 Oslo
Tlf: + 47 254 923
info.sanfarma@sanfarma.com

Österreich
SanFarma Generics
Nußdorfer Straße 33
A-2156 Wien
Tel: + 43 (0) 456 11888
Sanfarma@info.de

Polska
SanFarma Polska Sp.
Wyszogrodzka 2
PL – 77 455 Plock
Tel.: + 48 55 69971
sanfarmapolska@sanfarma.com

Portugal
SanFarma Farmacéuticos
São Domingo de Pedreira 578
P-4958-257 Odivelas
Tel: + 351 5956 223
informacao@sanfarma.com

România
SanFarma Pharmaceuticals
Strada Lungă 44
Sibiu 560220 – RO
Tel: + 40 200 551
sanfarmaromania@sanfarma.com

Slovenija
SanFarma d.d.
Trešnjevka-sjever 3
SI-1000 Zagreb
Tel: + 386 5623 66
sanfarma_slovenia@sanfarma.com

Slovenská republika
SanFarma Slovakia
Hlavná 2566/11
SK-070 02 Prešov
Tel: + 421 45213665
sanfarma_sk@sanfarma.com

Suomi/Finland
SanFarma Oy
Tapparakatu 166
FIN-80512 Juensuu
Puh/Tel: + 358 45657
info_dk@sanfarma.com

Sverige
SanFarma
Vaksealgatan 34
S-256 22 Uppsala
Tel: + 46 (0) 12345646
info_dk@sanfarma.com

United Kingdom
SanFarma UK
49 Walton Street
Oxford OX3 2JH UK
Tel: + 44 (0) 1856 2311
drugsafety@sanfarma.co.uk

Diese Packungsbeilage wurde zuletzt überarbeitet im November 2011.

Weitere Informationsquellen
Ausführliche Informationen zu diesem Arzneimittel sind auf den Internetseiten der Europäischen Arzneimittel-Agentur http://www.ema.europa.eu/ verfügbar. Sie finden dort auch Links zu anderen Internetseiten über seltene Erkrankungen und Behandlungen.

Diese Packungsbeilage ist auf den Internetseiten der Europäischen Arzneimittel-Agentur in allen EU-Amtssprachen verfügbar.

Appendix 8: English short text package leaflet with model template

Please read this package leaflet carefully!

Enal 20 mg tablets

1. What is Enal used for

- to treat high blood pressure
- to treat heart failure
- prevent development of heart failure in patients with reduced function of the left heart ventricle

2. What you must know before taking Enal

Do not take in the case of

- allergy to ingredients of Enal or medicines whose names end in -pril
- severe tissue swelling during previous use of similar medicines
- tendency to tissue swelling of deeper skin layers
- pregnancy

Consult your doctor before taking Enal in the case of

- risk of an excessive drop in blood pressure due to a disturbance in the electrolyte and fluid balance in the body
- narrowing of the heart valves of your left ventricle
- reduced blood circulation in the heart or brain
- reduced kidney function
- narrowed blood vessels in the kidney
- following a kidney transplant
- jaundice or an increase in liver enzyme values
- reduced number of white blood cells
- disease of the connective tissue involving blood vessels
- diabetes
- occurrence of a persistent, dry cough
- risk of an increase in blood potassium
- insufficient reduction in blood pressure especially in patients with a darker skin colour
- treatment to weaken allergy to insect venom
- use of special membranes for dialysis
- removal of blood fats with dextran sulphate
- prior to an operation or anaesthetic, including at the dentist
- breast-feeding
  Only use Enal during breast-feeding if the doctor decides it is absolutely necessary.

Taking other medicines

Tell your doctor or pharmacist if you are taking or have recently taken other medicines. This applies in particular to:

- medicines to increase water output through your kidneys
- potassium containing preparations
- heparin: a medicine to inhibit blood coagulation
- other blood pressure reducing medications
- allopurinol: a medicine to reduce uric acid levels
- lithium: a medicine to treat depression
- other medicines to treat depression or mental illness
- procainamide: a medicine to treat heart rhythm disorders
- narcotics or anaesthetics
- medicines to treat pain, inflammation and fever, such as acetylsalicyclic acid, ibuprofen, diclofenac
- medicines with an effect on the activity system, such as to:
  – increase blood pressure or heart frequency
  – widen the airways
- blood sugar reducing medicines and insulin
- medicines which supress the immune system

Food and drink

Do not drink alcohol.

Driving and using machines

Only drive or operate machines after consulting your doctor. Treatment with Enal can affect your reaction time.

3. How to take Enal

Take Enal exactly as your doctor has told you.

High blood pressure

Starting dose: ¼ tablet once daily or a lower dose
Usual daily dose: 1 tablet once daily
Maximum daily dose: 1 tablet twice daily

Heart failure and prevention

Use lower dose tablets for the starting dose!
Usual daily dose: 1 tablet once daily
Maximum daily dose: 1 tablet twice daily

Patients with kidney problems and patients over 65 years

Dose is dependent on kidney function.

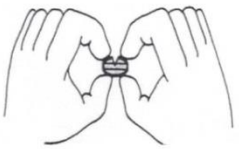
Children under 18 years

Enal should only be used in children to treat high blood pressure. However, newborns and children with kidney disease should be excluded from treatment.

- 20 to 50 kg body weight
  Use lower dose tablets for the starting dose!
  Maximum daily dose: 1 tablet once daily
- over 50 kg body weight
  Starting dose: ¼ tablet once daily
  Maximum daily dose: 1 tablet twice daily

Method of use

- sitting or standing with a glass of water with at least 100 ml content
- a time gap to meals is not required
- division of the tablet when necessary due to dose: see picture!



Duration of use

- determined by your doctor

Taking too much Enal

Inform your doctor immediately.

Forgotton dose

Do not take a double dose and continue taking Enal as prescribed.

Stopped use

Only stop use when directed by a doctor. Stopping treatment or altering dose without consulting your doctor reduces the efficacy or increases the risk of consequential damage.

4. Possible side effects

Studies show that the benefits of Enal prevail with the correct use.

Frequencies of side effects:
Very common, affects more than 1 in 10 people

- blurred vision
- dizziness
- cough
- nausea
- feeling of weakness

Common, affects 1 to 10 per 100 people
- usually painful, **severe swelling of lower tissue layers**, often in the face
  You require immediate medical treatment if you have tissue swelling of the larynx and/or tongue
- headache, depression
- fall in blood pressure when standing up, fainting
- heart attack, stroke
- chest pain, tightness in the chest
- disturbances of heart rhythm, accelerated pulse
- breathlessness
- diarrhea, abdominal pain, taste disturbance
- rash
- tiredness
- too much blood potassium or creatinine

Uncommon, affects 1 to 10 per 1000 people
- shortage of red blood cells
- low blood sugar levels
- confusion, nervousness
- somnolence, insomnia
- abnormal sensations
- palpitations
- increased mucous secretion from the nose
- sore throat, hoarseness
- spasms of the muscles in the airways, asthma
- intestinal obstruction
- inflammation of the pancreas
- vomiting, disturbed digestion, constipation
- lack of appetite, stomach irritation
- dry mouth
- stomach ulcer
- excessive sweating
- itching, nettle rash
- hair loss
- kidney dysfunction, kidney failure, protein in the urine
- impotence
- muscle cramps
- facial redness, fever
- feeling of unwellness
- noises in the ears
- increase in blood urea levels, decrease in blood sodium levels

Rare, affects 1 to 10 per 10,000 people
- reduced number of certain white blood cells, swollen lymph nodes
  Inform your doctor immediately if **fever, swelling of the lymph nodes** and/or **sore throat** occur so the white blood cell count can be investigated.
- **jaundice, increase in liver enzyme values**
  Discontinue treatment with Enal immediately and inform your doctor if jaundice or a marked increase in liver enzyme values occur.
- various, **severe forms of skin rash** with fever and blister formation
  Discontinue treatment with Enal immediately and inform your doctor if you suspect a serious skin reaction.
- lack of red blood pigment
- reduced bone marrow function
- immune system diseases
- abnormal dreams, sleep disturbances
- circulatory problems in fingers and feet
- distinctive features in the lung tissue
- runny nose
- allergic inflammation of the lungs
- inflammation of the mucous membrane in the mouth or tongue
- liver failure, inflammation of the liver
- reduced excretion of urine
- breast development in men

Very rare, affects less than 1 per 10,000 people
- swelling of the tissue in the intestine

Always inform your doctor or pharmacist if you notice side effects.

5. How to store Enal
- inaccesible to children
- do not use after the expiry date on the label or container
- do not store above 25°C

Enal is prescribed only for you. Do not give it to other people, even if they have similar complaints.

6. Further information
Composition
One tablet contains:
- active ingredient:
  20 mg Enalapril maleate.
- other ingredients:
  croscarmellose sodium, iron oxide, iron(III)oxide, lactose monohydrate, magnesium stearate, maize starch, sodium hydrogen carbonate.

Manufacturer
SanFarma
Sonnenstraße 1
D-12345 Sonne
Tel: 0423/233345
Fax: 0423/23344
Sanfarma@info.de

Information last updated
11/2011

Appendix 9: English short text package leaflet with QRD template 7.3.1

PACKAGE LEAFLET: INFORMATION FOR THE USER

Enal 20 mg tablets

Enalapril maleate

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT ENAL IS AND WHAT IT IS USED FOR

Enal is an ACE inhibitor, which means a medicine with the characteristics that it can lower blood pressure and provide support for the heart.

Enal is used:
- to treat high blood pressure
- to treat heart failure
- to prevent development of heart failure in patients with reduced function of the left heart ventricle.

2. BEFORE YOU TAKE ENAL

Do not take Enal
- if you are hypersensitive (allergic) to enalapril, medicines whose names end in -pril, or any of the other ingredients of Enal
- if severe tissue swelling has occurred during previous use of similar medicines
- if you have a tendency to tissue swelling of deeper skin layers
- during pregnancy

Take special care with Enal
- if you are at risk of an excessive drop in blood pressure due to a disturbance in the electrolyte and fluid balance in the body
- if you have a narrowing of the heart valves of your left heart ventricle
- if you suffer from reduced blood circulation in the heart or brain
- if your kidney function is reduced
- if you have narrowed blood vessels in the kidney
- following a kidney transplant
- if you have jaundice or increased liver enzyme values
- if you have a reduced number of white blood cells
- if you have disease of the connective tissue involving blood vessels
- if you suffer from diabetes
- if a persistent, dry cough develops
- if you are at risk of an increase in blood potassium
- if you have an insufficient reduction in blood pressure especially in patients with a darker skin colour
- if you are receiving treatment to weaken allergy to insect venom
- if you need to use special membranes for dialysis
- if your blood fats are being removed with dextran sulphate
- if you are going to have an operation or anaesthetic, including at the dentist
- if you are breast-feeding
  Only use Enal during breast-feeding if the doctor decides it is absolutely necessary.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This applies in particular to:
- medicines to increase water output through your kidneys
- potassium containing preparations
- heparin: a medicine to inhibit blood coagulation
- other blood pressure reducing medications
- allopurinol: a medicine to reduce uric acid levels
- lithium: a medicine to treat depression
- other medicines to treat depression or mental illness
- procainamide: a medicine to treat heart rhythm disorders
- narcotics or anaesthetics
- medicines to treat pain, inflammation and fever such as acetylsalicylic acid, ibuprofen, diclofenac
- medicines with an effect on the activity system such as to:
  – increase blood pressure or heart frequency
  – widen the airways
- blood sugar reducing medicines and insulin
- medicines which supress the immune system

Taking Enal with food and drink

Do not drink alcohol.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.
Pregnancy:
You should not take Enal during pregnancy.
Breast-feeding:
Only use Enal during breast-feeding if the doctor decides it is absolutely necessary.

Driving and using machines

Only drive or operate machines after consulting your doctor. Treatment with Enal can affect your reaction time.

Important information about some of the ingredients of Enal

This medicine contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, seek your doctor's advice before taking this medicinal product.

3. HOW TO TAKE ENAL

Always take Enal exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
The usual dose is unless otherwise prescribed by a doctor:

High blood pressure
Starting dose: ¼ tablet once daily or a lower dose
Usual daily dose: 1 tablet once daily
Maximum daily dose: 1 tablet twice daily

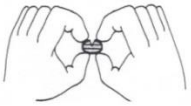
Heart failure and prevention
Use lower dose tablets for the starting dose!
Usual daily dose: 1 tablet once daily
Maximum daily dose: 1 tablet twice daily

Patients with kidney problems and patients over 65 years
Dose is dependent on kidney function.

Use in children

Enal should only be used in children to treat high blood pressure. However, newborns and children with kidney disease should be excluded from treatment.
- 20 to 50 kg body weight
  Use lower dose tablets for the starting dose!
  Maximum daily dose: 1 tablet once daily
- over 50 kg body weight
  Starting dose: ¼ tablet once daily
  Maximum daily dose: 1 tablet twice daily

Method of use
- sitting or standing with a glass of water with at least 100 ml content.
- a time gap to meals is not required
- division of the tablet when necessary due to dose: see picture!



Duration of use
- determined by your doctor

If you take more Enal than you should

Inform your doctor immediately.

If you forget to take Enal

Do not take a double dose to make up for a forgotten dose.

If you stop taking Enal

Only stop use when directed by a doctor. Stopping treatment or altering dose without consulting your doctor reduces the efficacy or increases the risk of consequential damage.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Enal can have side effects, although not everybody gets them.

During the evaluation of side effects, the following frequencies have been defined:

Very common	more than 1 in 10 patients treated
Common	less than 1 in 10, but more than 1 in 100 patients
Uncommon	less than 1 in 100, but more than 1 in 1000 patients
Rare	less than 1 in 1000, but more than 1 in 10,000 patients
Very rare	less than 1 in 10,000 patients, or unknown

Very common side effects
- blurred vision
- dizziness
- cough
- nausea
- feeling of weakness

Common side effects
- headache, depression
- fall in blood pressure when standing up, fainting
- heart attack, stroke
- chest pain, tightness in the chest
- disturbances of heart rhythm, accelerated pulse
- breathlessness
- diarrhea, abdominal pain, taste disturbance
- rash
- tiredness
- usually painful, severe swelling of lower tissue layers, often in the face
- too much blood potassium or creatinine

Uncommon side effects
- shortage of red blood cells
- low blood sugar levels
- confusion, nervousness
- somnolence, insomnia
- abnormal sensations
- palpitations
- increased mucous secretion from the nose
- sore throat, hoarseness
- spasms of the muscles in the airways, asthma
- intestinal obstruction
- inflammation of the pancreas
- vomiting, disturbed digestion, constipation
- lack of appetite, stomach irritation
- dry mouth
- stomach ulcer
- excessive sweating
- itching, nettle rash
- hair loss
- kidney dysfunction, kidney failure, protein in the urine
- impotence
- muscle cramps
- facial redness, fever
- feeling of unwellness
- noises in the ears
- increase in blood urea levels, decrease in blood sodium levels

Rare side effects
- reduced number of certain white blood cells, swollen lymph nodes
- lack of red blood pigment
- reduced bone marrow function
- immune system diseases
- abnormal dreams, sleep disturbances
- circulatory problems in fingers and feet
- distinctive features in the lung tissue
- runny nose
- allergic inflammation of the lungs
- inflammation of the mucous membrane in the mouth or tongue
- liver failure, inflammation of the liver, jaundice, increase in certain liver values
- various, severe forms of skin rash with fever and blister formation
- reduced excretion of urine
- breast development in men

Very rare side effects
- swelling of the tissue in the intestine

Countermeasures
Stop taking Enal immediately and inform your doctor if you suspect a serious skin reaction.
You require immediate medical treatment if you have tissue swelling of the larynx and/or tongue.
Stop taking Enal immediately and inform your doctor in the case of jaundice or increased liver enzymes.
Inform your doctor immediately if fever, swelling of the lymph nodes and/or throat inflammation occur so that the white blood cell count can be investigated.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE ENAL
Keep out of the reach and sight of children.
Do not use Enal after the expiry date which is stated on the label or container after EXP. The expiry date refers to the last day of the month.
Do not store above 25°C.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION
What Enal contains:
- The active substance is: Enalapril maleate.
  One tablet contains 20 mg Enalapril maleate.
- The other ingredients are: croscarmellose sodium, iron oxide, iron(III)oxide, lactose monohydrate, magnesium stearate, maize starch, sodium hydrogen carbonate.

What Enal looks like and contents of the pack:
Round, yellowish tablets; Packets with 30, 50 and 100 tablets.

Marketing Authorisation Holder and Manufacturer
SanFarma
Sonnenstraße 1
D-12345 Sonne
Tel: 0423/233345
Fax: 0423/23344
Sanfarma@info.de

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
SanFarma S.A
Rue de La Monnaie 24
B-1500 Bruxelles
Tél/Tel: + 32 (0) 800 56 456
SFBelgium_info@sanfarma.com

България
ЗАНФАРМА
Bul. Todor Slivnista Г
ЗВГИ СоФия
Тел.: + 359 4567656
info-sf@sanfarma.com

Česká republika
SanFarma Pharmaceuticals CR
Moskevská 7
CZ Praha
Tel: +420 255366
sfarma_cr@sanfarma.com

Danmark
SanFarma Denmark A/S
Tarp Hovedvej 12
DK-5277 Esbjerg
Tlf: + 45 567893
info_dk@sanfarma.com

Deutschland
SanFarma
Sonnenstraße 1
D-12345 Sonne
Tel: + 49 (0) 423/233345
Sanfarma@info.de

Eesti
SanFarma Baltics Eesti Filiaal
Telliskivi plats 3
EE – 10564 Kesklinn
Tel: +372 567523
Sanfarmaeesti@sanfarma.com

Ελλάδα
SanFarma Ελλάς
Αλεάνδ□ου
GR-457 77 Παλαμάξ
Τηλ: + 30 5669 222
info@sanfarma.gr

España
SanFarma S.L.U.
Calle de los Riato 12
E-75421 Montilla del Palancar
Tel: + 34 5669 111
info@sanfarma.es

France
SanFarma France
Rue de la Loire 34
F-24985 Tours
Tél: + 33 (0) 25 665544
contact@sanfarma-france.com

Ireland
SanFarma Ireland
89 Dromore Street
IRL - Banbridge BT34 5JH
Tel: + 353 (0) 5662333
info_ireland@sanfarma.com

Ísland
SanFarma
Tjarnagata 78
IS-105 Reykjavík
Sími: + 354 5622366
isregulatory@sanfarma.com

Italia
SanFarma Italy S.p.A.
Via Tuscolana 33
I-54896 Roma
Tel: + 39 (0) 3562 112
info@s-farma.com

Κύπρος
SanFarma Ελλάς
Σπύρολλ.
CY-000 00 Γαρίου
Τηλ: + 30 45433 11
cyprus_info@sanfarma.com

Latvija
SanFarma Latvijā
Liela lela 44
Jelgava, LV-1256
Tel: + 371 453 222
Info_lv@sanfarma.com

Lietuva
SanFarma Baltics
Perkūno alėja 44
LT 44301 Kaunas
Tel: +370 564 232
info_lietuva@sanfarma.com

Luxembourg/Luxemburg
SanFarma S.A.
Route d'Eich 66
L-1510 Luxembourg
Tél/Tel: + 32 (0) 800 56 456
SFBelgium_info@sanfarma.com

Magyarország
SanFarma Magyarország Zrt
Attila hid 8
H-5688 Budapest
Tel.: + 36 569 599
service.hungary@sanfarma.com

Malta
SanFarma Ελλάς
Triq Il-Konti 666
MT-4596 San Qormi
Tel: + 356 234588
info_malta@sfarma.com

Nederland
SanFarma Nederland B.V.
De la Meppelweg 25
NL-5663 AA Den Haag
Tel: + 31 (0) 453 1189
info.sanfarma-nl@sanfarma.com

Norge
SanFarma Norway A.S.
Grünerløkka 3
N-9548 Oslo
Tlf: + 47 254 923
info.sanfarma@sanfarma.com

Österreich
SanFarma Generics
Nußdorfer Straße 33
A-2156 Wien
Tel: + 43 (0) 456 11888
Sanfarma@info.de

Polska
SanFarma Polska Sp.
Wyszogrodzka 2
PL – 77 455 Plock
Tel.: + 48 55 69971
sanfarmapolska@sanfarma.com

Portugal
SanFarma Farmacéuticos
São Domingo de Pedreira 578
P-4958-257 Odivelas
Tel: + 351 5956 223
informacao@sanfarma.com

România
SanFarma Pharmaceuticals
Strada Lungă 44
Sibiu 560220 – RO
Tel: + 40 200 551
sanfarmaromania@sanfarma.com

Slovenija
SanFarma d.d.
Trešnjevka-sjever 3
SI-1000 Zagreb
Tel: + 386 5623 66
sanfarma_slovenia@sanfarma.com

Slovenská republika
SanFarma Slovakia
Hlavná 2566/11
SK-070 02 Prešov
Tel: + 421 45213665
sanfarma_sk@sanfarma.com

Suomi/Finland
SanFarma Oy
Tapparakatu 166
FIN-80512 Juensuu
Puh/Tel: + 358 45657
info_dk@sanfarma.com

Sverige
SanFarma
Vaksealgatan 34
S-256 22 Uppsala
Tel: + 46 (0) 12345646
info_dk@sanfarma.com

United Kingdom
SanFarma UK
49 Walton Street
Oxford OX3 2JH UK
Tel: + 44 (0) 1856 2311
drugsafety@sanfarma.co.uk

This leaflet was last approved in 11/2011.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

Appendix 10: English short text package leaflet with QRD template 8

Package leaflet: Information for the patient

Enal 20 mg tablets

Enalapril maleate

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What Enal is and what it is used for

Enal contains enalapril. It is an ACE inhibitor, which means a medicine with the characteristics that it can lower blood pressure and provide support for the heart.

Enal is used:
- to treat high blood pressure
- to treat heart failure
- to prevent development of heart failure in patients with reduced function of the left heart ventricle

This medicine helps to lower blood pressure which is useful in the prevention of complications which are caused by high blood pressure.

2. What you need to know before you take Enal

Do not take Enal:
- if you are allergic to Enalapril, medicines whose names end in –pril or any of the other ingredients of this medicine (listed in section 6).
- if severe tissue swelling has occurred during previous use of similar medicines
- if you have a tendency to tissue swelling of deeper skin layers
- during pregnancy

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking Enal in the case of:
- risk of an excessive drop in blood pressure due to a disturbance in the electrolyte and fluid balance in the body
- narrowing of the heart valves of your left ventricle
- reduced blood circulation in the heart or brain
- reduced kidney function
- narrowed blood vessels in the kidney
- following a kidney transplant
- jaundice or an increase in liver enzyme values
- reduced number of white blood cells
- disease of the connective tissue involving blood vessels
- diabetes
- occurrence of a persistent dry cough
- risk of an increase in blood potassium
- insufficient reduction in blood pressure especially in patients with a darker skin colour
- treatment to weaken allergy to insect venom
- use of special membranes for dialysis
- removal of blood fats with dextran sulphate
- prior to an operation or anaesthetic, including at the dentist
- breast-feeding:

Only use Enal during breast-feeding if the doctor decides it is absolutely necessary.

Children and adolescents

Enal should only be used in children to treat high blood pressure. However, newborns and children with kidney disorders should be excluded from treatment.

Other medicines and Enal

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This applies in particular to:
- medicines to increase water output through your kidneys
- potassium containing preparations
- heparin (a medicine to inhibit blood coagulation)
- other blood pressure reducing medications
- allopurinol (a medicine to reduce uric acid levels)
- lithium (a medicine to treat depression)
- other medicines to treat depression or mental illness
- procainamide (a medicine to treat heart rhythm disorders)
- narcotics or anaesthetics
- medicines to treat pain, inflammation and fever such as acetylsalicylic acid, ibuprofen, diclofenac
- medicines with an effect on the activity system to:
  - increase blood pressure or heart frequency
  - widen the airways
- blood sugar reducing medicines and insulin
- medicines which supress the immune system

Enal with food, drink and alcohol

Do not drink alcohol

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy:
You should not take Enal during pregnancy.

Breast-feeding:
Only use Enal during breast-feeding if the doctor decides it is absolutely necessary.

Driving and using machines

Only drive or operate machines after consulting your doctor. Treatment with Enal can affect your reaction time.

Enal contains Lactose

If you have been told by your doctor that you have an intolerance to some sugars, seek your doctor's advice before taking this medicinal product.

3. How to take Enal

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.
The recommended dose is:

High blood pressure

Starting dose: ¼ tablet once daily or a lower dose
Usual daily dose: 1 tablet once daily
Maximum daily dose: 1 tablet twice daily

Heart failure and prevention

Use lower dose tablets for the starting dose!
Usual daily dose: 1 tablet once daily
Maximum daily dose: 1 tablet twice daily

Patients with kidney problems and patients over 65 years

Dose is dependent on kidney function.

Use in children and adolescents

Enal should only be used in children to treat high blood pressure. However newborns and children with kidney disease should be excluded from treatment.
- 20 to 50 kg body weight
  Use lower dose tablets for the starting dose!
  Maximum daily dose: 1 tablet once daily
- over 50 kg body weight
  Starting dose: ¼ tablet once daily
  Maximum daily dose: 1 tablet twice daily

Method of use
- sitting or standing with a glass of water with at least 100 ml content.
- a time gap to meals is not required
- the tablet can be divided into equal doses
- division of the tablet when necessary due to dose: see picture!

Duration of use
- determined by your doctor

If you take more Enal than you should

Inform your doctor immediately.

If you forget to take Enal

Do not take a double dose to make up for a forgotten tablet.

If you stop taking Enal

Only stop use when directed by a doctor. Stopping treatment or altering dose without consulting your doctor reduces the efficacy or increases the risk of consequential damage.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Common: may affect up to 1 in 10 people
- usually painful, severe swelling of lower tissue layers, often in the face
  You require immediate medical treatment if you have tissue swelling of the larynx and/or tongue

Rare: may affect up to 1 in 1,000 people
- reduced number of certain white blood cells, swollen lymph nodes
  Inform your doctor immediately if fever, swelling of the lymph nodes and/or sore throat occur so the white blood cell count can be investigated.
- jaundice, increase in certain liver values
  If you develop jaundice or the liver enzyme values markedly increase, treatment must be discontinued and inform your doctor.
- various severe forms of skin rash with fever and blister formation
  If you suspect a serious skin reaction, consult your doctor and discontinue treatment with Enal immediately.

Other side effects
Very common: may affect more than 1 in 10 people
- blurred vision
- dizziness
- cough
- nausea
- feeling of weakness

Common: may affect up to 1 in 10 people
- headache, depression
- fall in blood pressure when standing up, fainting
- heart attack, stroke
- chest pain, tightness in the chest
- disturbances of heart rhythm, accelerated pulse
- breathlessness
- diarrhea, abdominal pain, taste disturbance
- rash
- tiredness
- too much blood potassium or creatinine

Uncommon: may affect up to 1 in 100 people
- shortage of red blood cells
- low blood sugar levels
- confusion, nervousness
- somnolence, insomnia
- abnormal sensations
- palpitations
- increased mucous secretion from the nose
- sore throat, hoarseness
- spasms of the muscles in the airways, asthma
- intestinal obstruction
- inflammation of the pancreas
- vomiting, disturbed digestion, constipation
- lack of appetite, stomach irritation
- dry mouth
- stomach ulcer
- excessive sweating
- itching, nettle rash
- hair loss
- kidney dysfunction, kidney failure, protein in the urine
- impotence
- muscle cramps
- facial redness, fever
- feeling of unwellness
- noises in the ears
- increase in blood urea levels, decrease in blood sodium levels

Rare: may affect up to 1 in 1,000 people
- lack of red blood pigment
- reduced bone marrow function
- immune system diseases
- abnormal dreams, sleep disturbances
- circulatory problems in fingers and feet
- distinctive features in the lung tissue
- runny nose
- allergic inflammation of the lungs
- inflammation of the mucous membrane in the mouth or tongue
- liver failure, inflammation of the liver
- reduced excretion of urine
- breast development in men

Very rare: may affect up to 1 in 10,000 people
- swelling of the tissue in the intestine

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

5. How to store Enal

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the label or container after EXP. The expiry date refers to the specified last day of that month.
Do not store above 25°C.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Enal contains

- The active substance is Enalapril maleate.
  One tablet contains 20 mg Enalapril maleate.
- The other ingredients (excipients) are croscarmellose sodium, iron oxide, iron(III)oxide, lactose monohydrate, magnesium stearate, maize starch, sodium hydrogen carbonate.

What Enal looks like and contents of the pack

Round, yellowish tablets; Packets with 30, 50 and 100 tablets.

Marketing Authorisation Holder and Manufacturer

SanFarma
Sonnenstraße 1
D-12345 Sonne
Tel: 0423/233345
Fax: 0423/23344
Sanfarma@info.de.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
SanFarma S.A
Rue de La Monnaie 24
B-1500 Bruxelles
Tél/Tel: + 32 (0) 800 56 456
SFBelgium_info@sanfarma.com

България
ЗАНФАРМА
Bul. Todor Slivnista Г
ЗВГИ СоФия
Тел.: + 359 4567656
info-sf@sanfarma.com

Česká republika
SanFarma Pharmaceuticals CR
Moskevská 7
CZ Praha
Tel: +420 255366
sfarma_cr@sanfarma.com

Danmark
SanFarma Denmark A/S
Tarp Hovedvej 12
DK-5277 Esbjerg
Tlf: + 45 567893
info_dk@sanfarma.com

Deutschland
SanFarma
Sonnenstraße 1
D-12345 Sonne
Tel: + 49 (0) 423/233345
Sanfarma@info.de

Eesti
SanFarma Baltics Eesti Filiaal
Telliskivi plats 3
EE – 10564 Kesklinn
Tel: +372 567523
Sanfarmaeesti@sanfarma.com

Ελλάδα
SanFarma Ελλάς
Αλεάνδ□ου
GR-457 77 Παλαμάς
Τηλ: + 30 5669 222
info@sanfarma.gr

España
SanFarma S.L.U.
Calle de los Riato 12
E-75421 Montilla del Palancar
Tel: + 34 5669 111
info@sanfarma.es

France
SanFarma France
Rue de la Loire 34
F-24985 Tours
Tél: + 33 (0) 25 665544
contact@sanfarma-france.com

Ireland
SanFarma Ireland
89 Dromore Street
IRL - Banbridge BT34 5JH
Tel: + 353 (0) 5662333
info_ireland@sanfarma.com

Ísland
SanFarma
Tjarnagata 78
IS-105 Reykjavík
Sími: + 354 5622366
isregulatory@sanfarma.com

Italia
SanFarma Italy S.p.A.
Via Tuscolana 33
I-54896 Roma
Tel: + 39 (0) 3562 112
info@s-farma.com

Κύπρος
SanFarma Ελλάς
Σπύρολλ
CY-000 00 Γαρίου
Τηλ: + 30 45433 11
cyprus_info@sanfarma.com

Latvija
SanFarma Latvijā
Liela Iela 44
Jelgava, LV-1256
Tel: + 371 453 222
Info_lv@sanfarma.com

Lietuva
SanFarma Baltics
Perkūno alėja 44
LT 44301 Kaunas
Tel: +370 564 232
info_lietuva@sanfarma.com

Luxemburg/Luxemburg
SanFarma S.A.
Route d'Eich 66
L-1510 Luxembourg
Tél/Tel: + 32 (0) 800 56 456
SFBelgium_info@sanfarma.com

Magyarország
SanFarma Magyarország Zrt
Attila hid 8
H-5688 Budapest
Tel.: + 36 569 599
service.hungary@sanfarma.com

Malta
SanFarma Ελλάς
Triq Il-Konti 666
MT-4596 San Qormi
Tel: + 356 234588
info_malta@sfarma.com

Nederland
SanFarma Nederland B.V.
De la Meppelweg 25
NL-5663 AA Den Haag
Tel: + 31 (0) 453 1189
info.sanfarma-nl@sanfarma.com

Norge
SanFarma Norway A.S.
Grünerløkka 3
N-9548 Oslo
Tlf: + 47 254 923
info.sanfarma@sanfarma.com

Österreich
SanFarma Generics
Nußdorfer Straße 33
A-2156 Wien
Tel: + 43 (0) 456 11888
Sanfarma@info.de

Polska
SanFarma Polska Sp.
Wyszogrodzka 2
PL – 77 455 Plock
Tel.: + 48 55 69971
sanfarmapolska@sanfarma.com

Portugal
SanFarma Farmacéuticos
São Domingo de Pedreira 578
P-4958-257 Odivelas
Tel: + 351 5956 223
informacao@sanfarma.com

România
SanFarma Pharmaceuticals
Strada Lungă 44
Sibiu 560220 – RO
Tel: + 40 200 551
sanfarmaromania@sanfarma.com

Slovenija
SanFarma d.d.
Trešnjevka-sjever 3
SI-1000 Zagreb
Tel: + 386 5623 66
sanfarma_slovenia@sanfarma.com

Slovenská republika
SanFarma Slovakia
Hlavná 2566/11
SK-070 02 Prešov
Tel: + 421 45213665
sanfarma_sk@sanfarma.com

Suomi/Finland
SanFarma Oy
Tapparakatu 166
FIN-80512 Juensuu
Puh/Tel: + 358 45657
info_dk@sanfarma.com

Sverige
SanFarma
Vaksealgatan 34
S-256 22 Uppsala
Tel: + 46 (0) 12345646
info_dk@sanfarma.com

United Kingdom
SanFarma UK
49 Walton Street
Oxford OX3 2JH UK
Tel: + 44 (0) 1856 2311
drugsafety@sanfarma.co.uk

This leaflet was last revised in November 2011.

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

Appendix 11: Questionnaire in English with possible correct answers used in the third round of the readability test

Anna Wolf
Am Boden 18
96215 Lichtenfels / Eichig
Germany

Improved medication leaflets – a research project

Lichtenfels, December 2012

Dear Sir/Madam,

Thank you very much for so generously giving of your time to participate in our project with the aim of improving medication leaflets. You will be pleased to know that we are now in the home straight, and the third and final; leaflet in the series is enclosed for your consideration and completion of the questionnaire.

Information leaflets from medicine packages are frequently criticised. The extended length of the text, too small a print size, scientific terms and long, complicated sentences are the most common complaints. Our goal is to improve package leaflets to the needs of the user.

This survey is anonymous.. Your task, as before, will be to complete a questionnaire to evaluate the package leaflet - how easy it is to understand and is it patient friendly? The results will assist you and many others to understand package leaflets with less difficulty in the future and thus achieve better health by using medication correctly.
We do not wish to test your general knowledge or your memory, but only the enclosed package leaflet. **Please answer all questions** in the questionnaire using the package leaflet provided and return it within 2 weeks. Answering the general questions below is beneficial for our evaluation.
We would like to thank you for your support.
Yours Sincerely
Anna Wolf

General questions about yourself: - please fill in all boxes -

Date of completion of questionnaire:……Postcode of residence:……...

Age:…… Gender: ……. First language: …….

- Level of education completed to date:

□ Primary School □ GCSE/GCE
□ A-level □ Technical college
□ University (number of years attended.....) □ Other

- Last practised occupation

……

- How many different pharmaceuticals do you take on average every day?

□ none, □ 1, □ 2, □ 3 to 4, □ 5 to 7, □ 8 to 10, □ more than 10

- Please list the pharmaceuticals you take regularly.

……

Each day, how long do you spend, on average, reading books, newspapers, magazines, etc? …… (hours)

In an average week, how many hours do you hear, read or see reports on medicines and medical treatments?……(hours)

Part 1: First read the entire package information leaflet and then answer the following questions referring to the leaflet as necessary. These questions are related to the medicine described in the leaflet. Tick the right-hand column if you are unable to find an answer in the leaflet.
Please note the **time** you need from start..... to finish..... to answer the following 26 questions.

Questions		Your answer	Please tick here if no answer was found.
1.	How should Enal be stored in relation to children?	Inaccessible to children	□
2.	What should you do, if you have taken too much Enal?	Contact a doctor	□
3.	Name the active substance in Enal?	Enalapril	□
4.	How frequent is the side effect 'hair loss'?	Uncommon or affects 1 to 10 people of 1000	□
5	What is the **starting dose** of Enal to treat high blood pressure in adults?	1/4 tablet once daily (comprised text) or once daily 5 mg (BfArM)	□
6.	Should women who think that they might be pregnant use this medicine?	No	□
7.	Should you give Enal to other people to use with a similar illness?	No	□
8.	Name one side effect which requires that you **immediately** contact your doctor.	Hypersensitivity reactions	□
9.	Can this tablet be divided?	Yes	□
10.	What should you do if you have just had a kidney transplant and you need Enal?	Consult your doctor	□
11.	Name one medicine that is used to treat heart rhythm disorders which can influence Enal.	procainamide	□
12.	What is Enal used to treat?	High blood pressure Heart failure	□
13	Can you take this medicine if you are allergic to lactose?	No	□
14.	What should you do if you want to stop taking this medicine?	Consult a doctor	□
15.	What should you do with regard to drinking alcohol when taking this medicine?	Not drink it	□

16.	How many people are affected by a side effect if it is ‘rare’? Please, write you answer in numbers, for example <...> of <.....> people	Either from table or other verbal descriptor	□
17.	Write down one reason why your ability to drive may be reduced due to taking Enal.	Reaction time is affected + side effects in Sect. 4	□
18.	What is Enal used for treating in children?	high blood pressure	□
19.	What should you do if you forget to take a dose of this medicine?	Not take the double dose	□
20.	What should you do if you need a dental operation while taking Enal?	Tell the dentist	□
21.	Is this medicine available with or without prescription by a doctor?	with	□
22.	What should you do if you already take medicines to reduce blood sugar levels and also need Enal?	Consult a doctor	□
23.	In which of the side effect frequency groups does the following frequency: ‘affects 5 in 100 people’ belong?	common	□
24.	What should you do if you notice the side effect runny nose?	Tell your doctor	□
25.	Under what circumstances may breast-feeding women take Enal?	‘Older nurslings’ (BfArM text) and ‘contraindicated’ comprised text	□
26	How long should Enal be used?	decided by the doctor	□

Please write the time at the top of the table!

Please go to part 2 overleaf.

Part 2: Below are different statements relating to the attached package leaflet. Please tick the boxes according to your opinion. – Only one tick per statement please! -

Statement		Your opinion				
		Yes	**mostly yes**	**Other**	**mostly no**	**not at all**
1.	The information requested in part 1 was easy to find.	□	□	□	□	□
2.	The first impression of this package leaflet motivated me to read further.	□	□	□	□	□
3.	The content of this package leaflet was difficult to understand.	□	□	□	□	□
4.	This package leaflet provided all the instructions I needed to use this medicine.	□	□	□	□	□
5.	Complicated sentences were used in this package leaflet.	□	□	□	□	□
6.	Each subheading clarifies the information contained in the following section.	□	□	□	□	□
7.	I feel well informed from the information contained within this package leaflet.	□	□	□	□	□
8.	This package leaflet contained too much information for me.	□	□	□	□	□
9.	The text is easy to read.	□	□	□	□	□
10.	The content of this package leaflet raises my concerns about using this medicine.	□	□	□	□	□
11.	This package leaflet contains difficult words.	□	□	□	□	□
12.	I found all information which is of importance to me at the beginning of this package leaflet.	□	□	□	□	□
13.	Some information about the medicine is missing from the package leaflet.	□	□	□	□	□
14.	Does the benefit of taking this medicine outweigh the potential risks?	□	□	□	□	□
15.	Would you like all package leaflets to be similar to this one?	□	□	□	□	□

Part 3: **Please write down:**

What do you like most about this package leaflet?

.....

What do you dislike most about this package leaflet?

.....

Which additional information do you think should be included in this package leaflet?

.....

Which information should be deleted in your opinion in the package leaflet? (Please mark in the package leaflet)

Thank you for your support!

Appendix 12: Questionnaire in German used in the third round of the readability test – The date was changed at the start of the questionnaire during each round of the readability test

Anna Wolf
Am Boden 18
96215 Lichtenfels / Eichig
Deutschland

Lichtenfels, Dezember 2012

Sehr geehrte Damen und Herren,

vielen herzlichen Dank, dass Sie so großzügig Ihre Zeit für die Teilnahme an unserem Projekt zur Verbesserung der Packungsbeilagen geopfert haben. Es wird Sie freuen zu hören, dass wir nun mit der dritten und letzten Beilage auf der Zielgeraden sind. Die beiliegende Seiten übergeben wir Ihnen nun zur Durchsicht und Vollendung des Fragebogens.

Packungsbeilagen von Arzneimitteln werden häufig kritisiert. Dabei gehören lange Texte, zu kleine Schriftgrößen, Fremdwörter und lange, komplizierte Sätze zu den häufigsten Problemen. Unser Ziel ist es, Packungsbeilagen den Wünschen und Bedürfnissen der Verbraucher anzupassen.
Diese Befragung ist anonym. Ihre Aufgabe besteht darin wie bisher, die Packungsbeilagen dahingehend zu bewerten, wie verständlich und patientenfreundlich sie sind. Die Ergebnisse sollen Ihnen und vielen anderen Menschen in der Zukunft den Umgang mit Packungsbeilagen erleichtern. In dieser Studie möchten wir nicht Ihr Allgemeinwissen oder Denkvermögen testen, sondern die Ihnen ausgehändigte Packungsbeilage. **Bitte beantworten Sie** deshalb **jede Frage** des Fragebogens unter Gebrauch der ausgehändigten Packungsbeilage innerhalb von zwei Wochen.
Für Ihre Unterstützung bedanken wir uns.
Mit freundlichen Grüßen
Anna Wolf

Allgemeine Angaben zu Ihrer Person: - Bitte füllen sie alle Felder aus! -
Datum, an dem der Fragebogen ausgefüllt wurde:..... Postleitzahl des Wohnortes: .....
Alter: .....Geschlecht: .....Muttersprache: .....
- abgeschlossene Ausbildung:
□ 8. Klasse □ 10. Klasse
□ Abitur □ Fachhochschule
□ Hochschule/Universität (Anzahl Hochschul/Unijahre.....) □ Andere
-Zuletzt ausgeübter Beruf .....
- Wie viele Medikamente wenden Sie durchschnittlich pro Tag an?
□ keine, □ 1, □ 2, □ 3 bis 4, □ 5 bis 7, □ 8 bis 10, □ mehr als 10
- Bitte geben Sie an, welche Medikamente Sie regelmäßig anwenden!
.....
Wie lange lesen Sie durchschnittlich pro Tag (Bücher, Zeitungen, Zeitschriften usw.)?..(Stunden)
Wie häufig hören, sehen oder lesen Sie medizinische Berichte pro Woche?..... (Stunden)

Teil 1: Lesen Sie bitte zuerst die gesamte Packungsbeilage und beantworten Sie danach die nachfolgenden Fragen. Diese Fragen beziehen sich auf den Inhalt der Packungsbeilage. Kreuzen Sie bitte in der rechten Spalte an, falls Sie keine Antwort in der Packungsbeilage finden konnten.
Geben Sie unbedingt die **Uhrzeit** von Beginn ..... und Ende ..... des Beantwortens der folgenden 26 Fragen des Fragebogens an.

Zu beantwortende Frage		**Ihre Antwort**	**Falls keine Antwort gefunden wurde, bitte hier ein Kreuz!**
1.	Wie sollte Enal in Bezug zu Kindern aufbewahrt werden?		☐
2.	Was sollten Sie tun, wenn Sie zu viel Enal eingenommen haben?		☐
3.	Nennen Sie den Wirkstoff von Enal?		☐
4.	Wie häufig tritt die Nebenwirkung „Haarausfall' auf?		☐
5	Was ist die **Anfangsdosis** von Enal zur Behandlung von Bluthochdruck bei Erwachsenen?		☐
6.	Sollten Frauen, die möglicherweise schwanger sind, dieses Arzneimittel einnehmen?		☐
7.	Sollten Sie Enal an andere Personen mit ähnlichen Krankheiten zum Gebrauch weitergeben?		☐
8.	Nennen Sie eine Nebenwirkung, die einen **sofortigen** Kontakt des Arztes erfordert.		☐
9.	Kann diese Tablette geteilt werden?		☐
10.	Was sollten Sie tun, wenn Sie kürzlich eine Nierentransplantation hatten und Enal einnehmen sollen?		☐
11.	Nennen Sie ein Arzneimittel, das zur Behandlung von Herzrhythmusstörungen verwendet wird und die Wirkung von Enal beeinflussen kann.		☐
12.	Wofür wird Enal angewendet?		☐
13	Dürfen Sie dieses Arzneimittel einnehmen, wenn Sie auf Laktose allergisch sind?		☐

14.	Was sollten Sie tun, wenn Sie die Einnahme dieses Arzneimittel beenden möchten?		□
15.	Wie sollten Sie sich hinsichtlich des Trinkens von Alkohol verhalten, wenn Sie dieses Arzneimittel einnehmen?		□
16.	Wie viele Personen sind von einer Nebenwirkung betroffen, wenn sie 'selten' ist? Bitte in **Zahlen** angeben, wie: <……> von <…….> Personen		□
17.	Nennen Sie einen Grund, weshalb Ihre Fahrtauglichkeit durch Einnahme von Enal verringert sein kann.		□
18.	Gegen welche Krankheit wird Enal bei Kindern verwendet?		□
19.	Was ist zu tun, wenn Sie die Anwendung dieses Medikamentes einmal vergessen haben?		□
20.	Was sollten Sie tun, wenn Sie eine Zahnoperation benötigen und Enal einnehmen?		□
21.	Ist das Medikament mit oder ohne ärztliche Verschreibung erhältlich?		□
22.	Was sollten Sie tun, wenn Sie bereits Arzneimittel zur Blutzuckersenkung einnehmen und Enal benötigen?		□
23.	Zu welcher Nebenwirkungsgruppe gehört folgende Häufigkeit: „betrifft 5 von 100 Personen'?		□
24.	Was sollten Sie tun, wenn Sie die Nebenwirkung Schnupfen feststellen?		□
25.	Wann dürfen stillende Frauen Enal einnehmen?		□
26	Wie lange sollte Enal angewendet werden?		□

Bitte Uhrzeit oberhalb der Tabelle eintragen!

Bitte gehen Sie nun zum Teil 2 auf der Rückseite!

Teil 2: Hier sind verschiedene Aussagen zu der Ihnen vorliegenden Packungsbeilage genannt. Bewerten Sie jede entsprechend Ihrer persönlichen Meinung. - Bitte immer nur eine Aussage ankreuzen! -

Zu bewertende Aussage		Ihre Meinung				
		ja	eher ja	trifft weder noch zu	eher nein	nein
1.	Die im Teil 1 erfragten Informationen konnte ich leicht im Text finden.	☐	☐	☐	☐	☐
2.	Mein erster Eindruck von der Packungsbeilage motiviert mich, sie zu lesen.	☐	☐	☐	☐	☐
3.	Der Text dieser Packungsbeilage ist schwer verständlich.	☐	☐	☐	☐	☐
4.	Diese Packungsbeilage erklärt mir ausreichend alle wichtigen Fragen zu diesem Arzneimittel.	☐	☐	☐	☐	☐
5.	In dieser Packungsbeilage wurden komplizierte Sätze verwendet.	☐	☐	☐	☐	☐
6.	Jede Zwischenüberschrift verdeutlicht, welche Informationen der folgende Abschnitt enthält.	☐	☐	☐	☐	☐
7.	Ich fühle mich durch diese Packungsbeilage über das Arzneimittel gut informiert.	☐	☐	☐	☐	☐
8.	Für mich sind zu viele Informationen in dieser Packungsbeilage enthalten.	☐	☐	☐	☐	☐
9.	Der Text ist für mich gut lesbar.	☐	☐	☐	☐	☐
10.	Der Inhalt dieser Packungsbeilage beängstigt mich, das Arzneimittel anzuwenden.	☐	☐	☐	☐	☐
11.	In dieser Packungsbeilage sind Fremdwörter enthalten.	☐	☐	☐	☐	☐
12.	Informationen, die mich sehr interessieren, sind zu Beginn in dieser Packungsbeilage enthalten.	☐	☐	☐	☐	☐
13.	In dieser Packungsbeilage fehlen mir Informationen zu diesem Arzneimittel.	☐	☐	☐	☐	☐
14.	Überwiegt der Nutzen dieses Arzneimittels die möglichen Gefahren?	☐	☐	☐	☐	☐
15.	Wünschen Sie sich, dass alle Packungsbeilagen so sind wie diese?	☐	☐	☐	☐	☐

Teil 3: Notieren Sie bitte:

Was finden Sie an dieser Packungsbeilage besonders gut?

.....

Was finden Sie an dieser Packungsbeilage besonders schlecht?

.....

Welche Informationen sollten Ihrer Meinung nach zusätzlich in diese Packungsbeilage aufgenommen werden?

.....

Welche Informationen sollten Ihrer Meinung nach nicht in der Packungsbeilage enthalten sein? (Bitte markieren Sie diese in der Packungsbeilage) **Vielen Dank für Ihre Unterstützung!**

Appendix 13: Results of the Wilcoxon test to identify significant differences between package leaflet versions for number of correct answers, wrong answers and not found answers for the 26 content questions of the readability test

Compared package leaflets (EN = English, DE = German)		Significance between leaflet versions		
		Correct answers	Wrong answers	Not found answers
EN-Model-template-short text	EN-QRD- template-7.3.1-short text	$p < 0.001$	$p < 0.001$	n.s
EN-Model- template-short text	EN-QRD- template-8-short text	$p < 0.001$	$p < 0.001$	n.s
EN-QRD- template-7.3.1-short text	EN-QRD- template-8-short text	$p < 0.001$	$p < 0.001$	n.s
DE-Model- template-short text	DE-QRD- template-7.3.1-short text	$p < 0.001$	$p < 0.001$	$p = 0.006$
DE-Model- template-short text	DE-QRD- template-8-short text	$p = 0.026$	$p < 0.001$	n.s
DE-QRD- template-7.3.1-short text	DE-QRD- template-8-short text	$p = 0.002$	$p < 0.001$	n.s
DE-Model- template-BfArM text	DE-QRD- template-7.3.1-BfArM text	$p = 0.001$	$p < 0.001$	$p < 0.001$
DE-Model- template-BfArM text	DE-QRD- template-8-BfArM text	n.s	$p < 0.001$	$p < 0.001$
DE-QRD- template-7.3.1-BfArM text	DE-QRD- template-8-BfArM text	$p < 0.001$	$p = 0.001$	n.s

Appendix 14: Results of the McNemar test to identify significant differences in the number of correct answers between short versions of the package leaflets in England (Only the results for the 5 of the 26 content questions which showed significant differences between different versions of the package leaflet are shown)

Compared package leaflets (EN = English)		**Question**				
		What should you do if you have just had a kidney transplant and you need Enal?	**Can you take this medicine if you are allergic to lactose?**	**What should you do if you need a dental operation while taking Enal?**	**In which of the side effect frequency groups does the following frequency: 'affects 5 in 100 people' belong?**	**What should you do if you notice the side effect runny nose?**
EN-Model-template-short text	EN-QRD-template-7.3.1-short text	$p < 0.001$	n.s	$p < 0.001$	$p = 0.001$	$p < 0.001$
EN-Model-template-short text	EN-QRD-template-8-short text	n.s	$p = 0.015$	$p = 0.002$	$p < 0.001$	$p = 0.012$
EN-QRD-template-7.3.1-short text	EN-QRD-template-8-short text	$p < 0.001$	n.s	$p < 0.001$	$p = 0.002$	$p < 0.001$

Appendix 15: Results of the McNemar test to identify significant differences in the number of correct answers between short versions of the package leaflets in Germany (Only the results for the 3 of the 26 content questions which showed significant differences between different versions of the package leaflet are shown)

Compared package leaflets (DE = German)		**Question**		
		What should you do if you have had a kidney transplant and you need Enal?	**What should you do if you need a dental operation while taking Enal?**	**In which of the side effect frequency groups does the following frequency 'affects 5 in 100 people' belong?**
DE-Model-template-short text	DE-QRD-template-7.3.1-short text	$p < 0.001$	$p < 0.001$	$p = 0.031$
DE-Model-template-short text	DE-QRD-template-8-short text	n.s	n.s	$p < 0.001$
DE-QRD-template-7.3.1-short text	DE-QRD-template-8-short text	$p < 0.001$	$p < 0.001$	$p < 0.001$

Appendix 16: Results of the McNemar test to identify significant differences in the number of correct answers between long versions of the package leaflets in Germany (Only the results for the 7 of the 26 content questions which showed significant differences between different versions of the package leaflet are shown)

Compared package leaflets (DE = German)		Question						
		How frequent is the side effect hairloss?	**Can this tablet be divided?**	**What should you do if you have had a kidney transplant and you need Enal?**	**What should you do if you want to stop taking this medicine?**	**In which of the side effect frequency groups does the following frequency 'affects 5 in 100 people' belong?**	**What should you do if you notice the side effect runny nose?**	**How long should Enal be used?**
DE-Model-template-BfArM text	DE-QRD-template 7.3.1-BfArM text	n.s	n.s	$p < 0.001$	n.s	$p = 0.018$	n.s	$p = 0.002$
DE-Model-template-BfArM text	DE-QRD-template-8-BfArM text	$p = 0.031$	$p = 0.001$	n.s	n.s	$p < 0.001$	$p = 0.009$	n.s
DE-QRD-template-7.3.1-BfArM text	DE-QRD-template-8-BfArM text	$p = 0.006$	$p = 0.024$	$p < 0.001$	$p = 0.035$	$p < 0.001$	n.s	n.s

Appendix 17: Results of the McNemar test to identify significant differences in the number of wrong answers between short versions of the package leaflets in England (Only the results for the 5 of the 26 content questions which showed significant differences between different versions of the package leaflet are shown)

Compared package leaflets (EN = English)		**Question**				
		What should you do if you have just had a kidney transplant and you need Enal?	**Can you take this medicine if you are allergic to lactose?**	**What should you do if you need a dental operation while taking Enal?**	**In which of the side effect frequency groups does the following frequency: 'affects 5 in 100 people' belong?**	**What should you do if you notice the side effect runny nose?**
EN-Model-template-short text	EN-QRD-template-7.3.1-short text	$p < 0.001$	$p = 0.004$	$p < 0.001$	$p = 0.002$	$p < 0.001$
EN-Model-template-short text	EN-QRD-template-8-short text	n.s	$p < 0.001$	n.s	$p < 0.001$	n.s
EN-QRD-template-7.3.1-short text	EN-QRD-template-8-short text	$p < 0.001$	n.s	$p < 0.001$	n.s	$p < 0.001$

Appendix 18: Results of the McNemar test to identify significant differences in the number of wrong answers between short versions of the package leaflets in Germany (Only the results for the 5 of the 26 content questions which showed significant differences between different versions of the package leaflet are shown)

Compared Package leaflets (DE = German)		**Question**				
		What should you do if you have just had a kidney transplant and you need Enal?	**Can you take this medicine if you are allergic to lactose?**	**What should you do if you need a dental operation while taking Enal?**	**In which of the side effect frequency groups does the following frequency: 'affects 5 in 100 people' belong?**	**What should you do if you notice the side effect runny nose?**
DE-Model-template-short text	DE-QRD-template 7.3.1-short text	$p < 0.001$	$p = 0.004$	$p < 0.001$	$p = 0.006$	n.s
DE-Model-template-short text	DE-QRD-template-8-short text	n.s	$p = 0.035$	n.s	$p < 0.001$	n.s
DE-QRD-template-7.3.1-short text	DE-QRD-template-8-short text	$p < 0.001$	n.s	$p < 0.001$	$p = 0.004$	$p = 0.008$

Appendix 19: Results of the McNemar test to identify significant differences in the number of wrong answers between long versions of the package leaflets in Germany (Only the results for the 4 of the 26 content questions which showed significant differences between different versions of the package leaflet are shown)

Compared package leaflets (DE = German)		**Question**			
		How frequent is the side effect 'hair loss'?	**What should you do if you have had a kidney transplant and you need Enal?**	**Can you take this medicine if you are allergic to lactose?**	**In which of the side effect frequency groups does the following frequency: 'affects 5 in 100 people' belong?**
DE-Model-template-BfArM text	DE-QRD-template 7.3.1-BfArM text	$p < 0.001$	$p < 0.001$	n.s	$p = 0.007$
DE-Model-template-BfArM text	DE-QRD-template-8-BfArM text	n.s	$p = 0.031$	$p < 0.001$	$p < 0.001$
DE-QRD-template-7.3.1-BfArM text	DE-QRD-template-8-BfArM text	$p < 0.001$	$p < 0.001$	n.s	$p = 0.013$

Appendix 20: Results of the McNemar test to identify significant differences in the number of not found answers between short versions of the package leaflets in England (Only the results for the 5 of the 26 content questions which showed significant differences between different versions of the package leaflet are shown)

Compared package leaflets (EN = English)		Question				
		What should you do if you have just had a kidney transplant and you need Enal?	**Can you take this medicine if you are allergic to lactose?**	**What should you do if you need a dental operation while taking Enal?**	**In which of the side effect frequency groups does the following frequency: 'affects 5 in 100 people' belong?**	**What should you do if you notice the side effect runny nose?**
EN-Model-template-short text	EN-QRD-template-7.3.1-short text	p = 0.021	p < 0.001	n.s	n.s	n.s
EN-Model-template-short text	EN-QRD-template-8-short text	p = 0.021	p < 0.001	p = 0.002	p = 0.013	p = 0.021
EN-QRD-template-7.3.1-short text	EN-QRD-template-8-short text	n.s	n.s	n.s	p = 0.049	p < 0.001

Appendix 21: Results of the McNemar test to identify significant differences in the number of not found answers between short versions of the package leaflets in Germany (Only the results for the 4 of the 26 content questions which showed significant differences between different versions of the package leaflet are shown)

Compared package leaflets (DE = German)		**Question**			
		Can you take this medicine if you are allergic to lactose?	**What should you do if you need a dental operation while taking Enal?**	**Is this medicine available with or without prescription by a doctor?**	**In which of the side effect frequency groups does the following frequency: 'affects 5 in 100 people' belong?**
DE-Model-template-short text	DE-QRD-template 7.3.1-short text	$p < 0.001$	$p = 0.016$	$p = 0.003$	n.s
DE-Model-template-short text	DE-QRD-template-8-short text	$p < 0.001$	n.s	$p = 0.035$	$p = 0.001$
DE-QRD-template-7.3.1-short text	DE-QRD-template-8-short text	n.s	n.s	n.s	$p < 0.001$

Appendix 22: Results of the McNemar test to identify significant differences in the number of not found answers between long versions of the package leaflets in Germany (Only the results for the 26 content questions which showed significant differences between different versions of the package leaflet are shown)

Compared package leaflets (DE = German)		Question				
		How frequent is the side effect 'hair loss'?	**What is the starting dose of Enal to treat high blood pressure in adults?**	**Name one side effect which requires that you immediately contact your doctor.**	**Can this tablet be divided?**	**What should you do if you have just had a kidney transplant and you need Enal?**
DE-Model-template-BfArM text	DE-QRD-template 7.3.1-BfArM text	p = 0.021	p = 0.022	p = 0.021	p = 0.029	n.s
DE-Model-template-BfArM text	DE-QRD-template-8-BfArM text	p = 0.021	n.s	p = 0.012	p < 0.001	p = 0.035
DE-QRD-template-7.3.1-BfArM text	DE-QRD-template-8-BfArM text	n.s	p < 0.001	n.s	n.s	p = 0.035

Appendix 23: Results of the McNemar test to identify significant differences in the number of not found answers between long versions of the package leaflets in Germany (Only the results for the 26 content questions which showed significant differences between different versions of the package leaflet are shown)

Compared package leaflets (DE = German)		Question				
		Can you take this medicine if you are allergic to lactose?	**What should you do with regard to drinking alcohol when taking this medicine?**	**In which of the side effect frequency groups does the following frequency: 'affects 5 in 100 people' belong?**	**What should you do if you notice the side effect runny nose?**	**How long should Enal be used?**
DE-Model-template-BfArM text	DE-QRD-template 7.3.1-BfArM text	$p < 0.001$	n.s	n.s	$p = 0.005$	$p = 0.007$
DE-Model-template-BfArM text	DE-QRD-template-8-BfArM text	$p < 0.001$	n.s	$p < 0.001$	$p = 0.004$	n.s
DE-QRD-template-7.3.1-BfArM text	DE-QRD-tempalte-8-BfArM text	n.s	$p = 0.008$	$p < 0.001$	n.s	n.s

Appendix 24: Results of the Pearson's chi-square test to identify significant differences in the time taken to answer the 26 content questions according to age group for the long versions of the package leaflet in Germany

Compared age group (years)		Significance
≤ 19	20 – ≤ 39	p < 0.001
≤ 19	40 – ≤ 59	p < 0.001
≤ 19	≥ 60	p < 0.001
20 – ≤ 39	40 – ≤ 59	n.s
20 – ≤ 39	≥ 60	p < 0.001
40 – ≤ 59	≥ 60	p < 0.001

Appendix 25: Results of the Pearson's chi-square test to identify significant differences in the time taken to answer the 26 content questions according to number of medicines taken per day for the long versions of the package leaflet in Germany

Compared number of medicines taken per day		Significance
0	1	n.s
0	2	$p < 0.001$
0	≥ 3	$p < 0.001$
1	2	$p = 0.016$
1	≥ 3	$p < 0.001$
2	≥ 3	n.s

Curriculum vitae

Name: Anna Wolf (nee Smith)

Date of birth: 23.11.1973

Place of birth: Cambridge, United Kingdom

Nationality: British

Marital status: Married, two children

School Education

1978 - 1985: Mayfield Primary School, Cambridge

1985 - 1990: Chesterton Community College, Cambridge

1990 - 1992: Long Road Sixth Form College, Cambridge (A - Levels)

University Education

1992 - 1996: London University, Imperial College of Science, Technology and Medicine.
Two terms at University of Bayreuth
Degree in Biology with first class honours

1996 - 1998: European Molecular Biology Laboratory, Heidelberg.
Master of Philosophy

Awards: Imperial College Governors Prize in Biology 1996

Memberships: Associate of the Royal College of Science

Employment History

1998 - 2000: University of Bayreuth, Assistant in the Department of Genetics

2000 - 2005: University of Bayreuth, Assistant in the Department of Microbiology

2006 - 2010: Dr. R. Pfleger Chemische Fabrik GmbH, Bamberg, Consultant for Drug Safety/Medical Information

Since 2010: Dr. R. Pfleger Chemische Fabrik GmbH, Bamberg, Project Manager for Medical Information

Author's declaration

I, Anna Wolf, born Smith, hereby confirm that according to Paragraph 8 of the doctoral degree regulations, that the presented work was completed independently and that no other source materials or aids were used other than those stipulated.

Eichig, the _____ (Anna Wolf)

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