The Influence of the European Union's QRD Template on the Use of Package Inserts Compared with a Shorter Model Template

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ABSTRACT

The number of words contained in package inserts used in the European Union has steadily increased. One reason for this trend is the expanding QRD template; a recommended framework for this patient information that consists of headings and general texts. The study referred to in this article investigated the advantages and disadvantages for package inserts using the QRD template, in comparison to a shorter model version.
Package inserts for three different medicines were printed in colour and also in black font using the QRD template and then the model template of less than 200 words. Each package insert was investigated using the written readability test method, consisting of a questionnaire containing 25 questions relating to the package inserts' contents. The 192 participants located the information and answered the questions over a timescale of 20 min (calculated median). However, they required 18.1 % more time (p=0.014) and located and understood 15.7 % less content (p=0.041) when using the QRD template. The advantage of the shorter model template illustrates that the QRD template's volume should be reduced – preferably to headings with less general texts.

ZUSAMMENFASSUNG

Einfluss des QRD-Templates der Europäischen Union auf den Gebrauch der Packungsbeilagen im Vergleich zu einem kürzeren Modell-Template

Die Wortanzahl der innerhalb der Europäischen Union verwendeten Packungsbeilagen ist stetig angestiegen. Ein Grund für diesen Trend ist die Ausdehnung des QRD-Templates – ein Textrahmen bestehend aus Überschriften und allgemeinen Texten, der für diese Patienteninformationen empfohlen wird. Die nachfolgende Studie untersuchte die Vor- und Nachteile dieses Templates im Vergleich zu einem kürzeren Modell-Template.
Packungsbeilagen von drei verschiedenen Arzneimitteln wurden je einmal mit farbiger und schwarzer Schrift erstellt unter Gebrauch des QRD-Templates und eines Modell-Templates mit weniger als 200 Wörtern. Jede Packungsbeilage wurde im schriftlichen Lesbarkeitstest-Verfahren, mit Hilfe eines Fragebogens untersucht, der 25 Fragen zum Inhalt der Packungsbeilagen enthielt. Die 192 Teilnehmer fanden die Informationen und beantworteten die Fragen innerhalb von 20 min (berechneter Median). Jedoch benötigten sie 18,1 % mehr Zeit (p = 0,014) bzw. fanden und verstanden sie 15,7 % weniger Informationen (p = 0,041), wenn das QRD-Template verwendet wurde. Die Vorteile des kürzeren Modell-Templates zeigen, dass der Textumfang des QRD-Templates gekürzt werden sollte – bevorzugt auf Überschriften und mit weniger allgemeinen Texten.

KEY WORDS

- Package insert
- Package insert test
- Patient information
- QRD template
- Readability test

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1. Introduction

Clear and easily understandable medicine package inserts are essential constituents in ensuring safe and successful therapeutic outcomes for patients [1–4]. Therefore, over time, various directives and guidelines were published worldwide in efforts to achieve a consistently high quality in comprehensibility, layout and design of patient information [5–10]. In some regions, including Australia and the European Union, text frameworks are additionally recommended [11,12].

The QRD template, generated by the Quality Review of Documents (QRD) Working Group – a part of the European Medicines Agency – is the required text frame

for use in European Union member states [12]. It considers the information order required by the European medicine act [9] and harmonises the wording for headings and general advices, thereby affording patients of each member state to experience a uniformity of structure in the package inserts of human medicines. This is easily possible as differences between the wording for medicines available only on prescription (Rx) and over-the-counter products (OTC), as well as the methods of approval – centralised and remaining procedures – are very minor, mainly affecting the beginning and the end of a package insert [12]. By contrast, the FDA currently confronts patients with three different information formats for medicines: consumer medication information, patient package inserts and Medication Guides. However, a drift towards a short "one-document solution" is afoot in the USA [13,14].

Although the QRD template does not provide specific information about medicines, it represents one major cause of text increase in package inserts in recent years [15]. A random selection of all package inserts available in Germany in 2005 showed that, on average, 355 of 2005 words contained in package inserts were caused by the template. This was before version 1.2 of October 2006 which increased the template to over 500 words and the updated version for centralised approved medicines published in July 2011, which increased the count to over 750 words [11,15,16].

However, the results of the PAINT1 study (PAINT: *pa*ckage *in*sert *t*est) illustrate that increasing the number of words is a major factor in decreasing patients' motivation to read and their ability to locate the provided information; whilst also reducing trust in using the medicines. Notably, the five package inserts with the official template, tested by 1105 participants in this written readability test study, displayed no advantages when compared to package inserts using a template with less than 200 words [4,17].

Despite the importance of the QRD template within the European Union, no significant surveys of it have been undertaken. Therefore, the following study was initiated to investigate the advantages and disadvantages of that template on package inserts when compared with a shorter version.

2. Material and methods

The package inserts of three widely used medicines – repaglinide, enalapril, insulin – were optimised using a set of 152 quality criteria [15] and printed in colour on light yellow paper and also in black on white paper using:

a) the QRD template version 1.2 [16] and
b) a model template based on the QRD template, but optimised to contain less than 200 words, mainly through avoiding repetitions and long sentences, akin to the PAINT1 study [4].

Each of the six pairs was identical in wording and design, except for the differences in the two templates (Fig. 1, Table 1).

The package inserts were investigated between September 2008 and May 2009 using the written readability test – also known as 'self-completion method' – as it is accepted within the European Union and removes any external negative influences which may occur in the Australian face-to-face interview [18]. The questionnaire from the PAINT1 study was used (one per medicine), in which the number of questions relating to the package inserts' key contents was increased from 15 to 25, with an 18th statement concerning participants' opinions of the package inserts in order to extract more data [4].

The participants were recruited in various public facilities – such as community centres – in Jena and Weimar (Germany). Each one tested just one package insert, using only the written instructions provided in the questionnaire, under one tester's supervision. In accordance with predefined criteria, minimum 15 people must be recruited per package insert version, with healthcare professionals excluded.

All data retrieved was coded and inserted into a SPSS 16.0 statistic program table via double data input for checking. Percentages of information not found and incorrectly comprehended as well as medians of the time required to locate the 25 key messages were calculated per package insert.

The five point scale listed under Table 1 was used to calculate medians for each of the 18 participants' assessments relating to the package inserts' comprehensibility, legibility, complexity of information, clarity and structure, as well as their trust in the relevant medicine.

3. Results

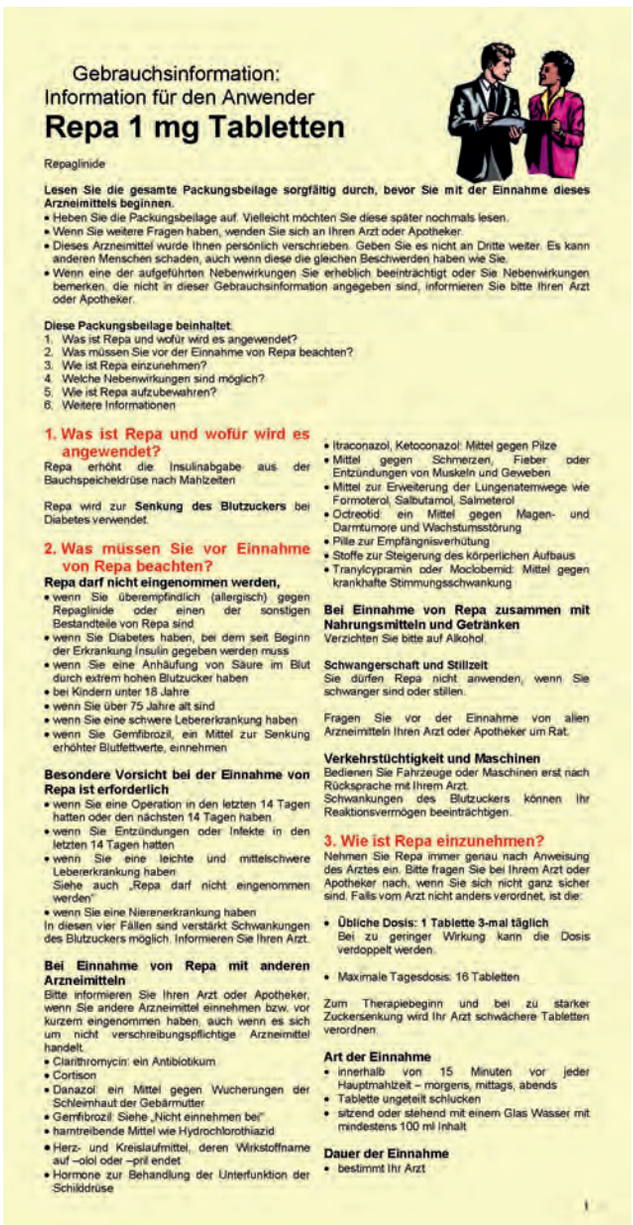
A total of 192 people aged between 11 and 79 years participated, with an average age of 34 years in both the group who tested the QRD template and the model template group. Half of the participants were female (52.1 %), 91.1 % spoke German as first language and 41.1 % used one or more medicines daily. On average, they read for 1 to 2 h daily and listened to, watched or read 1 medical report weekly. The education levels were: 8th class 12.4 %, 10th class 32.3 %, A-level 40.3 %, technical college 9.1 % and university 5.9 %. Significant differences between the group who tested the QRD template compared to the model template group were not found (age: Mann-Whitney U test; remaining demographic data: Pearson's chi-square test).

It took between 5 and 75 min (calculated median: 20 min) for participants to locate the 25 requested contents and to write their answers. Table 1 shows that 18.1 % more time was required when using the QRD template ($p=0.014$; Mann-Whitney U test). Furthermore, the QRD template caused a significant 15.7 % more answers 'not found' or 'incorrect' in comparison to the model template ($p=0.041$; Mann-Whitney U test); mainly difficulties of comprehensibility (Table 1).

Table 2 shows that 14.1 % of the incorrect answers from the QRD template group were caused by comprehensibility problems with the template wording, in comparison to 2.4 % from the group using the model template.

Thirty-three out of the 37 incorrect answers caused through the QRD template wording (Table 2) resulted from misunderstanding of the precaution/special warning section heading "Take special care with...", as people stated

a)



Gebrauchsinformation:
Information für den Anwender

Repa 1 mg Tabletten

Repaglinide

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

1. Was ist Repa und wofür wird es angewendet?

Repa erhöht die Insulinabgabe aus der Bauchspeicheldrüse nach Mahlzeiten

Repa wird zur **Senkung des Blutzuckers** bei Diabetes verwendet.

2. Was müssen Sie vor Einnahme von Repa beachten?

Repa darf nicht eingenommen werden,
- wenn Sie überempfindlich (allergisch) gegen Repaglinide oder einen der sonstigen Bestandteile von Repa sind
- wenn Sie Diabetes haben, bei dem seit Beginn der Erkrankung Insulin gegeben werden muss
- wenn Sie eine Anhäufung von Säure im Blut durch extrem hohen Blutzucker haben
- bei Kindern unter 18 Jahre
- wenn Sie über 75 Jahre alt sind
- wenn Sie eine schwere Lebererkrankung haben
- wenn Sie Gemfibrozil, ein Mittel zur Senkung erhöhter Blutfettwerte, einnehmen

Besondere Vorsicht bei der Einnahme von Repa ist erforderlich
- wenn Sie eine Operation in den letzten 14 Tagen hatten oder den nächsten 14 Tagen haben
- wenn Sie Entzündungen oder Infekte in den letzten 14 Tagen hatten
- wenn Sie eine leichte und mittelschwere Lebererkrankung haben
  Siehe auch „Repa darf nicht eingenommen werden"
- wenn Sie eine Nierenerkrankung haben

In diesen vier Fällen sind verstärkt Schwankungen des Blutzuckers möglich. Informieren Sie Ihren Arzt.

Bei Einnahme von Repa 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.
- Clarithromycin: ein Antibiotikum
- Cortison
- Danazol: ein Mittel gegen Wucherungen der Schleimhaut der Gebärmutter
- Gemfibrozil: Siehe „Nicht einnehmen bei"
- harntreibende Mittel wie Hydrochlorothiazid
- Herz- und Kreislaufmittel, deren Wirkstoffname auf –olol oder –pril endet
- Hormone zur Behandlung der Unterfunktion der Schilddrüse
- Itraconazol, Ketoconazol: Mittel gegen Pilze
- Mittel gegen Schmerzen, Fieber oder Entzündungen von Muskeln und Geweben
- Mittel zur Erweiterung der Lungenatemwege wie Formoterol, Salbutamol, Salmeterol
- Octreotid: ein Mittel gegen Magen- und Darmtumore und Wachstumsstörung
- Pille zur Empfängnisverhütung
- Stoffe zur Steigerung des körperlichen Aufbaus
- Tranylcypramin oder Moclobemid: Mittel gegen krankhafte Stimmungsschwankung

Bei Einnahme von Repa zusammen mit Nahrungsmitteln und Getränken

Verzichten Sie bitte auf Alkohol.

Schwangerschaft und Stillzeit

Sie dürfen Repa nicht anwenden, wenn Sie schwanger sind oder stillen.

Fragen Sie vor der Einnahme von allen Arzneimitteln Ihren Arzt oder Apotheker um Rat.

Verkehrstüchtigkeit und Maschinen

Bedienen Sie Fahrzeuge oder Maschinen erst nach Rücksprache mit Ihrem Arzt.
Schwankungen des Blutzuckers können Ihr Reaktionsvermögen beeinträchtigen.

3. Wie ist Repa einzunehmen?

Nehmen Sie Repa 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: 1 Tablette 3-mal täglich**
  Bei zu geringer Wirkung kann die Dosis verdoppelt werden.
- Maximale Tagesdosis: 16 Tabletten

Zum Therapiebeginn und bei zu starker Zuckersenkung wird Ihr Arzt schwächere Tabletten verordnen.

Art der Einnahme
- innerhalb von 15 Minuten vor jeder Hauptmahlzeit – morgens, mittags, abends
- Tablette ungeteilt schlucken
- sitzend oder stehend mit einem Glas Wasser mit mindestens 100 ml Inhalt

Dauer der Einnahme
- bestimmt Ihr Arzt

1

b)

Lesen Sie bitte aufmerksam die Packungsbeilage!

Repa 1 mg Tabletten

1. Wofür wird Repa verwendet?
- zur **Senkung des Blutzuckers** bei Diabetes

Wirkweise: Repa erhöht die Insulinabgabe aus der Bauchspeicheldrüse nach Mahlzeiten

2. Was müssen Sie vor Einnahme von Repa beachten?

Nicht einnehmen bei
- Überempfindlichkeit gegen einen Bestandteil von Repa
- Diabetes, bei dem seit Beginn der Erkrankung Insulin gegeben werden muss
- Anhäufung von Säure im Blut durch extrem hohen Blutzucker
- Schwangerschaft
- Stillzeit
- Kindern unter 18 Jahre
- Menschen über 75 Jahre
- schwerer Lebererkrankung
- Einnahme von Gemfibrozil: ein Mittel zur Senkung erhöhter Blutfettwerte

Informieren Sie Ihren Arzt bei
- Operation in den letzten oder nächsten 14 Tagen
- Entzündungen und Infekten in den letzten 14 Tagen
- leichte und mittelschwere Lebererkrankung
  Siehe auch „Nicht einnehmen bei"
- Nierenerkrankung

In diesen vier Fällen sind verstärkt Schwankungen des Blutzuckers möglich.

Einnahme mit anderen Arzneimitteln

Reden Sie mit Ihrem Arzt oder Apotheker bei Gebrauch anderer Arzneimittel in den letzten 14 Tagen. Dies gilt besonders bei:
- Clarithromycin: ein Antibiotikum
- Cortison
- Danazol: ein Mittel gegen Wucherungen der Schleimhaut der Gebärmutter
- Gemfibrozil: Siehe „Nicht einnehmen bei"
- harntreibende Mittel wie Hydrochlorothiazid
- Herz- und Kreislaufmittel, deren Wirkstoffname auf –olol oder –pril endet
- Hormone zur Behandlung der Unterfunktion der Schilddrüse
- Itraconazol, Ketoconazol: Mittel gegen Pilze
- Mittel gegen Schmerzen, Fieber oder Entzündungen von Muskeln und Geweben
- Mittel zur Erweiterung der Lungenatemwege wie Formoterol, Salbutamol, Salmeterol
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Nahrungsmittel und Getränke

Verzichten Sie bitte auf Alkohol.

Verkehrstüchtigkeit und Maschinen

Bedienen Sie Fahrzeuge oder Maschinen erst nach Rücksprache mit Ihrem Arzt.
Schwankungen des Blutzuckers können Ihr Reaktionsvermögen beeinträchtigen.

3. Wie ist Repa einzunehmen?

Nehmen Sie Repa **immer** nach Anweisung Ihres Arztes ein.
- **Übliche Dosis: 1 Tablette 3-mal täglich**
  Bei zu geringer Wirkung kann die Dosis verdoppelt werden.
- Maximale Tagesdosis: 16 Tabletten

Zum Therapiebeginn und bei zu starker Zuckersenkung wird Ihr Arzt schwächere Tabletten verordnen.

Art der Einnahme
- innerhalb von 15 Minuten vor jeder Hauptmahlzeit – morgens, mittags, abends
- Tablette ungeteilt schlucken
- sitzend oder stehend mit einem Glas Wasser mit mindestens 100 ml Inhalt

Dauer der Einnahme
- bestimmt Ihr Arzt

1

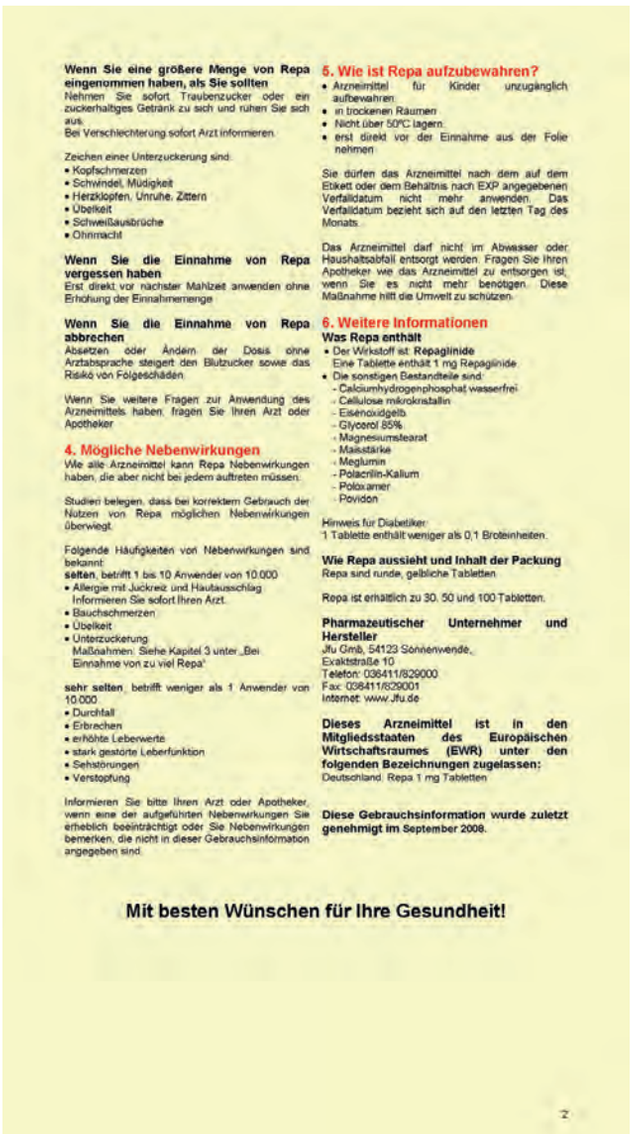
Figure 1 A: Example of a package insert using the QRD template and the corresponding package insert using the model template tested in this study. a) Repaglinide package insert (colour) using the QRD template (page 1). b) Repaglinide package insert (colour) using the model template (page 1).

that they have to take special care, but failed to provide actions should precautionary aspects apply to them.

Another error, the misunderstanding in the enalapril package insert that lactose is the active substance, which occurred in the QRD template version, was caused by the Excipients Guideline wording at the end of the package insert chapter 2 [12,19]. Although the model template package inserts only contained the names of the active substances in chapter 6, there was no significant difference between the groups in the percentage who correctly provided the names of the active substances (QRD template 95.8 %; model template 94.6 %).

On ten occasions parts of repaglinide's action mechanism were mistakenly classified as the indication, a consequence of the QRD template and the European medicine act requiring that the less important action mechanism must be stated before the more important indication [9,12]. However, the action mechanism was provided after the indication in the model template, reducing the occurrences of this error to just two (Table 2).

a)



Wenn Sie eine größere Menge von Repa eingenommen haben, als Sie sollten
Nehmen Sie sofort Traubenzucker oder ein zuckerhaltiges Getränk zu sich und ruhen Sie sich aus.
Bei Verschlechterung sofort Arzt informieren.

Zeichen einer Unterzuckerung sind:
- Kopfschmerzen
- Schwindel, Müdigkeit
- Herzklopfen, Unruhe, Zittern
- Übelkeit
- Schweißausbrüche
- Ohnmacht

Wenn Sie die Einnahme von Repa vergessen haben
Erst direkt vor nächster Mahlzeit anwenden ohne Erhöhung der Einnahmemenge.

Wenn Sie die Einnahme von Repa abbrechen
Absetzen oder Ändern der Dosis ohne Arztabsprache steigert den Blutzucker sowie das Risiko von Folgeschäden.

Wenn Sie weitere Fragen zur Anwendung des Arzneimittels haben, fragen Sie Ihren Arzt oder Apotheker.

4. Mögliche Nebenwirkungen

Wie alle Arzneimittel kann Repa Nebenwirkungen haben, die aber nicht bei jedem auftreten müssen.

Studien belegen, dass bei korrektem Gebrauch der Nutzen von Repa möglichen Nebenwirkungen überwiegt.

Folgende Häufigkeiten von Nebenwirkungen sind bekannt:
selten, betrifft 1 bis 10 Anwender von 10.000
- Allergie mit Juckreiz und Hautausschlag
  Informieren Sie sofort Ihren Arzt.
- Bauchschmerzen
- Übelkeit
- Unterzuckerung
  Maßnahmen: Siehe Kapitel 3 unter „Bei Einnahme von zu viel Repa"

sehr selten, betrifft weniger als 1 Anwender von 10.000
- Durchfall
- Erbrechen
- erhöhte Leberwerte
- stark gestörte Leberfunktion
- Sehstörungen
- Verstopfung

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 Repa aufzubewahren?

- Arzneimittel für Kinder unzugänglich aufbewahren.
- in trockenen Räumen
- Nicht über 50°C lagern.
- erst direkt vor der Einnahme aus der Folie nehmen

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.

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 Repa enthält
- Der Wirkstoff ist: **Repaglinide**
  Eine Tablette enthält 1 mg Repaglinide.
- Die sonstigen Bestandteile sind:
  - Calciumhydrogenphosphat wasserfrei
  - Cellulose mikrokristallin
  - Eisenoxidgelb
  - Glycerol 85%
  - Magnesiumstearat
  - Maisstärke
  - Meglumin
  - Polacrilin-Kalium
  - Poloxamer
  - Povidon

Hinweis für Diabetiker:
1 Tablette enthält weniger als 0,1 Broteinheiten.

Wie Repa aussieht und Inhalt der Packung
Repa sind runde, gelbliche Tabletten.

Repa ist erhältlich zu 30, 50 und 100 Tabletten.

Pharmazeutischer Unternehmer und Hersteller
Jfu GmbH, 54123 Sonnenwende,
Exaktstraße 10
Telefon: 036411/829000
Fax: 036411/829001
Internet: www.Jfu.de

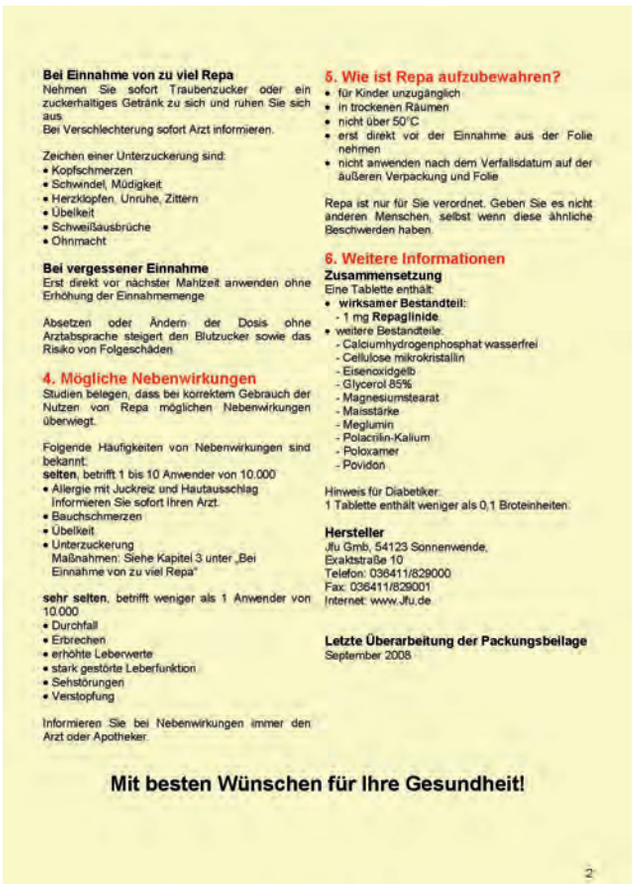
Dieses Arzneimittel ist in den Mitgliedsstaaten des Europäischen Wirtschaftsraumes (EWR) unter den folgenden Bezeichnungen zugelassen:
Deutschland: Repa 1 mg Tabletten

Diese Gebrauchsinformation wurde zuletzt genehmigt im September 2008.

Mit besten Wünschen für Ihre Gesundheit!

2

b)



Bei Einnahme von zu viel Repa
Nehmen Sie sofort Traubenzucker oder ein zuckerhaltiges Getränk zu sich und ruhen Sie sich aus.
Bei Verschlechterung sofort Arzt informieren.

Zeichen einer Unterzuckerung sind:
- Kopfschmerzen
- Schwindel, Müdigkeit
- Herzklopfen, Unruhe, Zittern
- Übelkeit
- Schweißausbrüche
- Ohnmacht

Bei vergessener Einnahme
Erst direkt vor nächster Mahlzeit anwenden ohne Erhöhung der Einnahmemenge.

Absetzen oder Ändern der Dosis ohne Arztabsprache steigert den Blutzucker sowie das Risiko von Folgeschäden.

4. Mögliche Nebenwirkungen

Studien belegen, dass bei korrektem Gebrauch der Nutzen von Repa möglichen Nebenwirkungen überwiegt.

Folgende Häufigkeiten von Nebenwirkungen sind bekannt:
selten, betrifft 1 bis 10 Anwender von 10.000
- Allergie mit Juckreiz und Hautausschlag
  Informieren Sie sofort Ihren Arzt.
- Bauchschmerzen
- Übelkeit
- Unterzuckerung
  Maßnahmen: Siehe Kapitel 3 unter „Bei Einnahme von zu viel Repa"

sehr selten, betrifft weniger als 1 Anwender von 10.000
- Durchfall
- Erbrechen
- erhöhte Leberwerte
- stark gestörte Leberfunktion
- Sehstörungen
- Verstopfung

Informieren Sie bei Nebenwirkungen immer den Arzt oder Apotheker.

5. Wie ist Repa aufzubewahren?

- für Kinder unzugänglich
- in trockenen Räumen
- nicht über 50°C
- erst direkt vor der Einnahme aus der Folie nehmen
- nicht anwenden nach dem Verfallsdatum auf der äußeren Verpackung und Folie

Repa ist nur für Sie verordnet. Geben Sie es nicht anderen Menschen, selbst wenn diese ähnliche Beschwerden haben.

6. Weitere Informationen

Zusammensetzung
Eine Tablette enthält:
- **wirksamer Bestandteil:**
  - 1 mg **Repaglinide**
- weitere Bestandteile:
  - Calciumhydrogenphosphat wasserfrei
  - Cellulose mikrokristallin
  - Eisenoxidgelb
  - Glycerol 85%
  - Magnesiumstearat
  - Maisstärke
  - Meglumin
  - Polacrilin-Kalium
  - Poloxamer
  - Povidon

Hinweis für Diabetiker:
1 Tablette enthält weniger als 0,1 Broteinheiten.

Hersteller
Jfu GmbH, 54123 Sonnenwende,
Exaktstraße 10
Telefon: 036411/829000
Fax: 036411/829001
Internet: www.Jfu.de

Letzte Überarbeitung der Packungsbeilage
September 2008

Mit besten Wünschen für Ihre Gesundheit!

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Figure 1 B: Example of a package insert using the QRD template and the corresponding package insert using the model template tested in this study. a) Repaglinide package insert (colour) using the QRD template (page 2). b) Repaglinide package insert (colour) using the model template (page 2).

Actions to be taken in the case that side effects occur were not located by 11.2 % of participants using the QRD template package inserts in comparison to 4.2 % when using the model template versions. The higher rate in the QRD template group is based on the longer sentence at the end of chapter 4 – the only difference to the model template package inserts – as it recommended contacting healthcare professionals only if side effects get serious.

Only five incorrect answers were caused by the model template wording. They were due to misunderstandings of the advice in the interaction section to: "Inform your doctor or pharmacist if you have used other medicines in the last 14 days." The five participants stated that they should wait 14 days, rather than informing their doctor should an interaction occur.

A second problem in the model template group occurred with an average 13.8 % of the participants not locating information relating to results if treatment is stopped too early; this compares with 4.2 % in the QRD template group where a subheading was used.

No other disadvantages based on compression of the template text were found. For example: participants correctly understood whether or not the medicine can be used during pregnancy similarly well in both template groups, although the model template provided such information as part of the special warning or contraindication lists (percentage of correct answers for QRD template group: 95.8 %, model template group: 97.8 %). Similar high percentages of correct answers were found relating to information about children and breast-feeding.

The correct decision regarding avoiding use of the medicine when a specific contraindication applies to the patient was made by 79.0 % of the participants in the QRD template group and 85.6 % in the model template group. Also, information relating to the most recent package insert update was located and understood com-

Table 1

Comparison of package inserts using the QRD template with those using a model template, in the time required to locate information, percentages of not located contents and misunderstood information, as well as participants' opinions calculated from 18 statements, itemised per package insert.

Package insert	Time needed to locate the 25 tested information [calculated medians in min]		Percentage of not located answers relating to the 25 content questions [average in %]		Percentage of incorrect answers of the located information [average in %]		Participants' opinions relating to the package insert [average]*		Number of words per package insert		Number of participants	
	QRD template	model template	QRD template	model template	QRD template	model template	QRD template	model template	QRD template	model template	QRD template	model template
Enalapril colour	25.0	18.5	9.7	3.2	12.7	6.6	1.9	2.0	1333	849	16	16
Insulin colour	25.0	25.0	8.2	7.3	14.9	10.2	2.0	2.0	1265	835	16	17
Repaglinide colour	20.0	15.4	3.2	4.2	13.4	7.0	2.0	1.7	1093	682	15	17
Enalapril black/white	20.0	16.7	8.2	9.3	12.4	10.7	1.8	2.0	1333	849	16	16
Insulin black/white	21.2	17.8	7.4	7.7	15.4	16.4	2.0	1.8	1265	835	16	15
Repaglinide black/white	22.0	19.4	3.0	7.2	9.0	9.3	1.7	2.0	1093	682	16	16
Average	*22.2*	*18.8*	*6.6*	*6.5*	*13.0*	*10.0*	*1.9*	*1.9*	*1230*	*789*	–	–

* Code of participants' opinions: "yes" = 1, "mostly yes" = 2, "other" = 3, "mostly no" = 4, and "no" = 5, whereby "yes" was the preferred answer.

Table 2

Incorrectly understood information of the located contents itemised per package insert and template group.

Package insert	Number of incorrect answers using the QRD template ... (n=95 participants)			Number of incorrect answers using the model template ... (n=97 participants)		
	in total	due to the template wording	due to the content order in chapter 1	in total	due to the template wording	due to the content order in chapter 1
Enalapril colour	38	5	–*	24	0	–*
Insulin colour	49	10	–*	37	1	–*
Repaglinide colour	47	6	4	28	1	0
Enalapril black/white	40	5	–*	36	0	–*
Insulin black/white	55	7	–*	53	1	–*
Repaglinide black/white	34	4	6	34	2	2
Total	*263*	*37*	*10*	*212*	*5*	*2*

* The action mechanism was stated for repaglinide only.

parably well with 95.8 % correct answers in the QRD template group and 100 % in the model template group, even though the text of the latter group was slightly shorter.

Participants' opinions relating to the package inserts were positive and comparable in both template groups (Table 1). This also applied to each of the 18 requested aspects, such as the motivation to read the package insert, volume of text, locatability and comprehensibility of information.

4. Discussion

The findings clearly illustrate the advantages of the shorter model template compared to the investigated QRD template, as patients locate required contents more quickly, while the shorter template text harbours fewer opportunities for misunderstandings.

Limitations due to the number of participants and the test method used are not expected, as the results are confirmed through the PAINT1 study involving five times as many participants. Furthermore, the written readability test method avoids external influences, such as caused by mimicking, gestures and hearing problems – unlike the Australian face-to-face verbal interview [18] – thereby guaranteeing identical study conditions for each participant, an essential requirement for comparing both templates. Influences on the results caused by non-participation of those with reading and writing difficulties are also unlikely, as identical test conditions applied to both templates and a minimum reading level is a basic requirement for using package inserts independent of the test method used.

Based on the authors' research and readability test experiences, major variations of the results when using other languages are also not anticipated. However, the advantages of the shorter model template might be curtailed in more extensive package inserts.

Opportunities for condensing the QRD template involve, for example, deleting repetitions, long sentences and the general information between the name of the medicine and package insert chapter 1. Although the QRD template states that some patients mentioned in readability tests that an index would be helpful [12], it is not essential. Well-emphasised headings and a clear layout represent an appropriate alternative, as found. However, where a pharmaceutical company assesses the requirement for an index, they should have the liberty to use one. Furthermore, deleting the remaining general information contained at the beginning of the template is possible, as it contains no specific contents required by the European medicines act and some points are repeated elsewhere in the template. These opportunities are confirmed through the investigation of a similar template in the PAINT1 study [4].

A template reduced mainly to short and meaningful headings would better meet patients' and healthcare professionals' requirements for shorter package inserts limited to essential information [20,21]. Moreover, existing research illustrates that reducing the number of words without deleting required information significantly improves package inserts [17,22-24]. Therefore, the authors recommend considering the results found with the model template (Fig. 2), as:

- all information demanded in the European medicine act [9] can be inserted in the required order, using a shorter text frame which is chiefly built on short headings,
- the QRD template is not a legally binding requirement according to the treaty on European Union, article 249 [25],
- the shorter model template is successfully tested, including side effect frequency explanations – here and in the PAINT1 study – unlike the QRD template.

5. The new QRD template, version 8

What inferences can be made on the updated QRD template from this study? In the following, advantages and disadvantages of the new template are discussed based on the findings, whereby further discussion of the updated template has been published previously [26].

5.1 Volume of text

Some text improvements aside, such as in the precaution and side effect sections, the number of words has increased in its entirety in the updated QRD template version 8 used for centralised approved Rx medicines to 752 words for the English text version (Fig. 2) and 771 words for OTC products (German translation: RX medicines: 795 words; OTC medicines: 818 words) [12]. However, these numbers do not include the option to mention 29 addresses of the local MAH representatives.

If the opportunity to delete all texts contained within pointed brackets were taken (= grey marked text in Fig. 2), the QRD template text would reduce to 257 words in the English version for Rx medicines – a volume of text similar to that of the model template (minimum: 173 words; maximum: 230 words including all side effect frequency explanations). Given the current situation whereby the QRD template text is usually used in its entirety in package inserts, a further increase in the number of words used in package inserts will ensue, thereby provoking the negative consequences already described in the introduction [15–17].

The results of this study and the facts provided in the previous chapter should stimulate pharmaceutical companies and agencies to use just the minimum requirement of QRD template text and to exclude the unnecessary list of 29 MAH representatives. For example, according to the QRD template's "bracketing convention", the entire paragraph before the index is not essential as it is framed in

QRD template version 8	Suggested template text based on the tested model template text
Package leaflet: Information for the <patient> <user> {(Invented) name strength pharmaceutical form} {Active substance(s)}	**Please, read this package leaflet carefully!** **{(Invented) name strength pharmaceutical form}**
<Read all of this leaflet carefully before you start <taking> <using> 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> <,> <or> <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> <,> <or> <pharmacist> <or nurse>. This includes any possible side effects not listed in this leaflet>.	
<Read all of this leaflet carefully before you start <taking> <using> this medicine because it contains important information for you. Always <take> <use> this medicine exactly as described in this leaflet or as your <doctor> <,> <or> <pharmacist> <or nurse> <has> <have> told you. – Keep this leaflet. You may need to read it again. – Ask your pharmacist if you need more information or advice. – 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 must talk to a doctor if you do not feel better or if you feel worse <after {number of} days>.>	
What is in this leaflet 1. What X is and what it is used for 2. What you need to know before you <take> <use> X 3. How to <take> <use> X 4. Possible side effects 5. How to store X 6. Contents of the pack and other information	
1. What X is and what it is used for <You must talk to a doctor if you do not feel better or if you feel worse <after {number of} days>.>	**1. What X is used for**
2. What you need to know before you <take> <use> X	**2. What you must know before <using> <taking> X**
Do not <take> <use> X<:> – <if you are allergic to {active substance(s)} or any of the other ingredients of this medicine (listed in section 6).>	**Do not <use> <take> in the case of** • allergy to ingredients of X • ...
Warnings and precautions Talk to your doctor <or> <,> <pharmacist> <or nurse> before <taking> <using> X	**Consult your doctor before <using> <taking> X in the case of** • ...
Children <and adolescents>	
Other medicines and X <Tell your <doctor> <or> <pharmacist> if you are <taking> <using>, have recently <taken> <used> or might <take> <use> any other medicines.>	**Using other medicines** Tell your doctor or pharmacist if you have recently used other medicines. This applies particularly to: • {to be completed with medicine names known to cause interactions}
X with <food> <and> <,> <drink> <and> <alcohol>	**<Food and drink>**

Figure 2 A.

Figure 2 A, B, C: Suggested template text for package inserts based on the tested model template translated into English after optimisation of two minor aspects described in chapters 5.3 and 5.4. Legend: X trade name of the medicine; <> texts to be used as required; {} explanation. Texts which are not marked with grey background are the minimum requirement.

QRD template version 8	Suggested template text based on the tested model template text
Pregnancy <and> <,> 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.>	
Driving and using machines	**Driving and using machines**
<X contains {name the excipient(s)}>	
3. How to <take> <use> X <Always <take> <use> this medicine exactly as your doctor <or pharmacist> has told you. Check with your <doctor> <or> <pharmacist> if you are not sure.>	**3. How to <use> <take> X** <Use> <Take> X exactly as your doctor has told you.
<The recommended dose is...>	{to be completed as required with:} <Starting dose:> <Usual dose:> <Maximum dose:>
Always <take> <use> this medicine exactly as described in this leaflet or as your <doctor> <,> <or> <pharmacist> <or nurse> <has> <have> told you. Check with your <doctor> <or> <,> <pharmacist> <or nurse> if you are not sure.>	**Method of use**
The recommended dose is...>	**Duration of use**
<Use in children <and adolescents>>	
<The score line is only there to help you break the tablet if you have difficulty swallowing it whole.> <The tablet can be divided into equal doses.> <The score line is not intended for breaking the tablet.>	
<If you <take> <use> more X than you should>	**<Using> <Taking> too much X**
<If you forget to <take> <use> X> <Do not take a double dose to make up for a forgotten <tablet> <dose> <...>.>	**Forgotten use** {to be completed with information relating to missing a dose}
<If you stop <taking> <using> X> <If you have any further questions on the use of this medicine, ask your <doctor> <,> <or> <pharmacist> <or nurse>.>	**<Stopped use>** {to be completed with information relating to stopping use of the medicine}
4. Possible side effects Like all medicines, this medicine can cause side effects, although not everybody gets them.	**4. Possible side effects** Studies show that the benefits of X prevail with the correct use.
<Additional side effects in children <and adolescents>>	Frequencies of side effects: <**Very common**, affects more than 1 per 10 users> • ... <**Common**, affects 1 to 10 per 100 users> • ... <**Uncommon**, affects 1 to 10 per 1,000 users> • ... <**Rare**, affects 1 to 10 per 10,000 users> • ... <**Very rare**, affects less than 1 per 10,000 users> • ... <**Frequency unknown**, according to the available data> • ... {Each frequency should only be used if required and the side effects inserted according to their frequencies}
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.	Always inform your doctor or pharmacist if you notice side effects.

Figure 2 B.

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QRD template version 8	Suggested template text based on the tested model template text
5. How to store X 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> <carton> <bottle> <...> <after {abbreviation used for expiry date}.> <The expiry date refers to the last day of that month.> <Do not use this medicine if you notice {description of the visible signs of deterioration}.> <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.>	**5. How to store X** Inaccessible to children. X is prescribed only for you. Do not give it to other people, even if they have similar complaints.
6. Contents of the pack and other information **What X contains** – The active substance(s) is (are)... – The other ingredient(s) <(excipient(s))> is (are)... **What X looks like and contents of the pack** **Marketing Authorisation Holder and Manufacturer** {Name and address} <{tel}> <{fax}> <{e-mail}> For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder: {list of 29 adresses of the local MAH representations} **This leaflet was last revised in** **<{MM/YYYY}> <{month YYYY}.>** <This medicine has been given 'conditional approval'. This means that there is more evidence to come about this medicine. The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.> <This medicine has been authorised under 'exceptional circumstances'. This means that <because of the rarity of this disease> <for scientific reasons> <for ethical reasons> it has been impossible to get complete information on this medicine. The European Medicines Agency will review any new information on this medicine every year and this leaflet will be updated as necessary.> **<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.> <----------> <The following information is intended for healthcare professionals only:>	**6. Further information** **Composition:** {to be completed as required, such as} {One tablet} contain<s>: • active substance<s>: • further ingredient<s>: **Manufacturer** **Information last updated** {MM/YYYY}

Figure 2 C.

pointed brackets (Notice: Of the 24 languages used, only in the German version are the pointed brackets missing). Indeed, a general recommendation exists to invite readers at the beginning of the information to read the text, through a description of what the leaflet is for and why it has been supplied [27]. However, as package inserts have been provided with medicines for some decades now within the European Union, it can reasonably be assumed that patients know why they are contained, similarly to instructions provided with other – such as technical –

products. Therefore, such an invitation is not necessary and results of this and the PAINT1 study show it does not increase patients' motivation to read package inserts [17].

5.2 Indications and active substances

Providing the less important pharmacotherapeutic group, or the action mechanism, before the very important indications causes more comprehensibility problems in comparison to the inversed order, this is a known aspect [4,21]. However, this order is part of Directive 2001/83/EC and can only be changed by an amendment to this directive. The use of subheadings in the first package insert chapter, as recommended in the annotated QRD template version 8, could be an acceptable compromise until the amendment of this directive.

The annotated version of the updated QRD template suggests providing the active substance names in package insert chapter 1 for a third time. This must be assessed as unnecessary, as results prove it is sufficient to list these ingredients in chapter 6 only. This is further confirmed through the PAINT1 study [4]. The active substance name repetition under the name of the medicine at the beginning of package inserts is a Directive 2001/83/EC, Article 59 (1) ai) requirement; however, this content "… shall be included where the product contains *only one* active substance *and* if its name is an *invented name*" [9]. The German medicine act demands this repetition if the product does not contain more than three active substances and the active substance names are not part of the medicine name [28].

5.3 Contraindications, precautions, interactions

The updated QRD template version 8 contains a new heading in the "Warnings and precautions" section and additionally, the action that patients should inform the doctor if anything listed in the paragraph applies to them. This is a significant improvement in comparison to the previous heading, "Take special care with X", as it provides a clear instruction which should avoid the problems with the previous QRD template found in this study. The model template contains a similar action for patients; however, provided as a subheading, using fewer words, similar to the contraindication subheading.

Another improvement in the updated QRD template, according to the results, is that bullet points in the contraindication and warnings/precautions sections should no longer begin with "if you…" or "when" as suggested in the previous version 7.3.1. The results of the model template show that these words are not necessary and the key messages can be provided without them at the beginning of each bullet point.

Information relating to pregnancy, breast-feeding, children and elderly was integrated in the model template group in the list of contraindication or warnings/precautions, as required. The results of this study and those of the PAINT1 study show that a subsection for this information is not essential. More important is that the contents are provided in the form of clear instructions. A separate short section to provide this information is appropriate; however, repetitions of the contents in other sections are not necessary. Furthermore, in a case where a subsection is used for information relating to children as well as elderly, we suggest specifying the age range of the respective group in the subheadings, such as "Children under 18 years" or "Adults over 65 years".

Based on this study, one suggested change in the model template concerns the interaction section, where "recently" should used instead of "the last 14 days" (Fig. 2). This measure should avoid the few problems found here, even though "recently" does not convey an exact time period.

5.4 Dosage instruction, application errors

Many adaptations concerning the dosage instruction chapter can be assessed as helpful for patients, such as clarifications relating to the dosage, method and duration of use. However, awareness must be maintained that information provided here should be limited to the essential points. Furthermore, a clear structure of the required information is essential. This could be in the form provided in Fig. 1 and the model template of Fig. 2.

The findings suggest a second amendment to the model template, namely the insertion of a short subheading relating to stopping use of the medicine if such information is required, such as in the case of Rx medicines that require regular use.

5.5 Side effects

Providing side effects with their frequency information supports patients in correctly classifying their importance. However, a numerical explanation of the frequency adjectives is essential as, without them, people often overestimate the occurrences of adverse drug reactions [4,29]. The updated QRD template recommends in the annotated version that this information should not be contained in a separate list at the beginning of package insert chapter 4. This will have a positive impact as using these explanations as subheading, similar to the examples provided in Fig. 1, better connects them with their respective side effects. However, the annotated template recommends a new explanation, such as "Common: may affect up to 1 in 10 people" instead of "affects more than 1 in 100 but less than 1 in 10". It justifies this change with "user testing has shown that double sided expressions ... are not well understood ..." [12]. The new QRD template frequency explanation is better understood than the provided previous example according to the PAINT3 study results – an investigation of 295 package inserts with 5091 participants – because it is shorter with less complex phrasing. However, the double-sided explanation used here – such as "Common, affects 1 to 10 per 100 users" (Fig. 1 and 2) – showed a significantly higher comprehensibility rate in the PAINT3 study than the new QRD template version [26]. This double-sided explanation was also successfully tested in the PAINT1 study and

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subsequently recommended by the EMA and patient/consumer organisations in 2007 [4,30]. The greater comprehensibility apart, it is important to note that the MedDRA frequency convention also demands double-sided explanations for the summary of product characteristics (SmPC), such as "Common (≥1/100 to <1/10)" [12; appendix II]. Directive 2001/83/EC, Article 59(1) states "The package leaflet shall be drawn up in accordance with the summary of the product characteristics" which declines using side effect frequency explanations published in the updated QRD template [9].

The instruction that patients should generally inform their healthcare professional if side effects occur represents a positive change in the updated QRD template. The new wording will avoid problems found here and in the PAINT1 study with texts contained in the previous QRD template; some people understood those to mean that they do not require any contact with experts if side effects are not serious or listed in the package insert [4]. However, the results with the model template show that a shorter advice is also sufficient.

6. Conclusion

The new QRD template version 8 contains many improvements in comparison to its previous version. However, there are still aspects which require further optimisation. One utterly important point is the number of words, as the shorter model template with around 200 words bears significant advantages compared to the longer QRD template. Therefore, it is recommended to limit the number of QRD template words in package inserts to those which are absolutely necessary – short headings with less general texts.

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