



Analysis of German package inserts*

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Abstract. Objective: Package inserts have an important impact on patients compliance and thus on the effectiveness of drug use. Despite efforts of the European or national regulatory authorities and manufacturers to improve the readability and comprehensiveness of package inserts, they are still the subject of critical discussion. **Material and methods:** 68 German package inserts were chosen for a detailed analysis of their quality and suitability based on a set of 104 quality criteria developed prior to the survey. **Results:** In many cases package inserts available on the German drug market did not include important information or were difficult to read or understand. In 73.5% of cases, the daily maximum dose was missing and 63.2% gave no information on the measures to take for each of the interactions. 66.2% of package inserts provided no instructions about the correct storage and 58.8% gave no instructions on the appropriate storage temperature. In 13 cases, dosage instructions were provided only in milligrams of active substance instead of a number of tablets or volume of liquid. 98.5% of the 68 package inserts included non-quantifiable statements such as “high dosage” or “take 2–4 tablets, 1–3 times daily”. 97.1% contained repetitious information, 83.8% included advertising elements and 8.8% contained contradictory information. **Conclusion:** Package inserts must be optimized and tested by selected groups of patients prior to approval of the drug. This will avoid misunderstandings and lack of information and ensure that use of the drug will give the best possible outcome and avoid safety risks.

Introduction

Package inserts are important because they provide essential drug information. They should inform patients about the drugs, improve the success of treatment and, in particular they should increase drug safety [EFPIA 2003, The European Parliament and the Council of the European Union 2001]. Direc-

tive 2001/83/EC of the European Parliament and the Council stipulates that in every Member State of the European Union all medicinal products for human use shall include a package insert [The European Parliament and the Council of the European Union 2001]. Package inserts are therefore one of the most frequently used sources of drug information. In surveys 70–85% of patients indicated that they always or often read the package inserts to inform themselves about their medicines [Fuchs et al. 2003, Vander Stichele et al. 1991, Weitbrecht and Vosskaemper 2002].

Despite the efforts by the European and national regulatory authorities and the manufacturers to improve the readability and comprehensibility of package inserts the usefulness of them is still under discussion. Important points of criticism include comprehension (because they often use highly technical words), the small font size and the extensive amount of information included [Bernardini et al. 2000, Fuchs et al. 2005]. Some articles report that reading package inserts can make patients uncertain about their therapy or stop them using their medication [Fuchs et al. 2003, Van Haecht et al. 1991, Vander Stichele et al. 1991].

The following survey was carried out to examine a number of aspects that influence the comprehensiveness and readability of package inserts. In addition, the availability of important patient information was also examined.

Method

A set of 104 quality criteria for evaluating package inserts were developed prior to the survey [Fuchs 2004]. The criteria included recommendations for package inserts based

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on the European and German drug laws [N.N. 1998, The European Parliament and the Council of the European Union 2001] and also included general instructions for easily understandable and clearly legible written information in the German language [Christmann and Groeben 1999, Hohgräwe 1988].

The rating pharmacist did not know the content and design of the 68 selected package inserts at the beginning of the survey. The analyzed versions were from:

- commonly used drugs (n = 68),
- products from different manufacturers (n = 36),
- drugs with different therapeutic indications (n = 43) and application forms (n = 19) and
- drugs available on the German market during the first 6 months of 2000 (n = 68).

All package inserts chosen were assigned to one of the following three groups:

- Group A: drugs with national registration in Germany and available only on prescription (n = 34, drugs of the 20 most prescribed therapeutic indication groups in Germany in 1997 [Schwabe and Pfaffrath 1999]),
- Group B: over-the-counter drugs with national registration in Germany (n = 23, frequently bought over-the-counter drugs in the first quarter in 1999 [IMS Health 1999]) and
- Group C: drugs with European registration, only available on prescription (n = 11, choice of available drugs at the time of the analysis [N.N. 1999]).

Results

Analysis of content

The date of last update in 89.7% of all package inserts was between 1997 and 1999. Four versions failed to include this information.

All package inserts contained information on therapeutic indication, contraindications, interactions, dosage instruction, possible adverse drug reactions and storage. However, an in-depth analysis using the 104 criteria revealed some differences:

Contraindications

5 package inserts failed to include specific instructions on measures necessary to deal with all the contraindications. Information on possible use during pregnancy was missing in four package inserts and in nine cases advice on use during lactation was missing.

Instructions on possible application to children and the elderly could only be found in 64.7% and 25.0% of all versions, respectively. Of these package inserts, 16 provided no information on the age of the children and 10 provided no information on the age group of the elderly. There were no significant differences between the three groups.

Interactions

Only 36.8% of all package inserts examined included recommendations on suitable measures for dealing with the listed interaction. Versions in Group A had significantly lower results in this quality criterion (13.3%) and versions in Group C the highest (100%).

Dosage instruction

All package inserts analyzed included information on the form of consumption and dosage of the medication. However, 13 of them provided dosage instructions only in milligrams of active substance instead of a unit dose such as 2 tablets or 1 capsule. Among the 68 package inserts, there were 29 cases with non-specific statements with regard to the dosage instructions (e.g. take 2–4 tablets, 1–3 times daily without an explanation as to the use of 2 or 4 tablets) (Table 1).

Only 26.5% of all versions included the maximum daily dose. Approximately three quarters of these (n = 18) gave this dosage instruction as a number of tablets or capsules or as volume (Table 1).

Advice on the period of use was available in 55 cases. Most (94.6%) included this information in the form of a number. 77.8% of package inserts for non-prescription drugs provided advice on when to consult a medical doctor.

39.7% of the 68 versions described the time of the day when the medication should be used. 48 of 56 inserts for oral-used prepa-

Table 1. Package inserts (n = 68) which meet the quality criteria of dosage instructions (selection of quality criteria; n.s. = not significant).

Quality criteria	All versions	Meet quality criteria Group			Differences (p*)		
		A	B	C	A/B	A/C	B/C
Dosage instructions are available	100% n = 68	100% n = 34	100% n = 23	100% n = 11	n.s.	n.s.	n.s.
All dosage instructions are given as number of tablets or capsules or as volume, drops or amount of the drug	80.6% n = 67	72.7% n = 33	91.3% n = 23	81.8% n = 11	n.s.	n.s.	n.s.
Non-quantifiable dosage as instructions such as 1 – 3 times, 2 – 4 tablets without an explanation are missing	57.4% n = 68	52.9% n = 34	43.5% n = 23	100% n = 11	n.s.	0.009	0.002
Information such as take the medicine "to", "before" or "independent" of a meal are available in the case of orally taken drugs	85.7% n = 56	85.7% n = 28	83.3% n = 18	90.0% n = 10	n.s.	n.s.	n.s.
The maximum daily dose is included	26.5% n = 68	23.5% n = 34	30.4% n = 23	27.3% n = 11	n.s.	n.s.	n.s.
The maximum daily dose is given as number of tablets, capsules or volume	72.2% n = 18	87.5% n = 8	71.4% n = 7	33.3% n = 3	n.s.	n.s.	n.s.
Hints on the period of use are available	80.9% n = 68	88.2% n = 34	78.3% n = 23	63.6% n = 11	n.s.	n.s.	n.s.
The type of solution to use is given for orally taken drugs with a solid application form	38.5% n = 39	29.4% n = 17	33.3% n = 12	60.0% n = 10	n.s.	n.s.	n.s.
The amount of solution to use is given by orally taken drugs with a solid application form	20.5% n = 39	29.4% n = 17	16.7% n = 12	10.0% n = 10	n.s.	n.s.	n.s.
Hints on the divisibility of orally taken drugs with solid application form are given	34.1% n = 41	61.1% n = 18	15.4% n = 13	10.0% n = 10	0.025	0.016	n.s.

*U-test (Mann and Whitney).

rations gave information such as: take the medicine "to", "before" or "independent" of a meal. Should the preparation be required to be taken before a meal, then a quantifiable time for consumption was given by only 20% (Table 1).

38.5% mentioned the kind of liquid to be used with solid medications (such as tablets or capsules) taken orally (n = 39) and only 20.5% included information on the amount of liquid. Recommendations that tablets and capsules should be taken in an upright position [Gallo et al. 1996] was missing in all cases (Table 1).

Whether it was possible to divide i.e. break oral preparations such as tablets was included in 34.1% of package inserts (Table 1).

Hints on application errors

If patients make administration errors, they will need information on suitable measures [The European Parliament and the Council of the European Union 2001]. In 10 cases however, this important information was missing.

Table 2. Means, minimums and maximums different aspects of the comprehensibility, readability and extent from package inserts (n = 68) (n.s. = not significant).

	All versions			Mean of the groups			Differences (p*)		
	mean	min	max	A	B	C	A/B	A/C	B/C
Foreign words of all words (%)	3.3	0.3	10.7	4.5	2.2	1.7	< 0.001	< 0.001	n.s.
Non-quantifiable statements in 100 sentences (n)	14	0	33	15.8	16.7	4.9	n.s.	< 0.001	< 0.001
Abbreviations in 100 sentences (n)	12	0	31	13.0	12.5	4.9	n.s.	< 0.001	= 0.001
Repetitions in package inserts (n)	3	0	18	4.4	2.5	2.7	= 0.001	0.021	n.s.
Brackets in 100 sentences (n)	34	7	81	42.4	29.3	16.6	0.007	< 0.001	0.005
Words in package inserts (n)	1,496	365	3,375	1,911	998	1,253	< 0.001	0.002	n.s.
Sentences in package inserts (n)	95	24	194	118	64	89	< 0.001	0.012	0.007
Sentences with more than 20 words (%)	19.3	6.8	36.7	20.9	19.0	15.2	n.s.	0.012	n.s.
Words with more than 20 letters (%)	0.9	0	3.7	1.1	1.1	0.3	n.s.	< 0.001	< 0.001
Number of advertising elements in package inserts (n)	1	0	3	0.9	1.1	0.9	n.s.	n.s.	n.s.
Font size (pt)	8	6	11	7.8	8.3	8.5	n.s.	0.008	n.s.
Paper weight (g/m ²)	53.0	40.0	133.5	51.3	52.9	58.2	n.s.	n.s.	n.s.

*U-test (Mann and Whitney).

In addition, only 40.0% and 55.6% of package inserts for drugs available only on prescription, Group A and C respectively, included information on possible side effects after stopping the medication or changing the dose without advice of a doctor.

Possible adverse drug reactions

Only one of the 68 inserts gave quantitative information in numbers regarding the frequency of application and nine versions included the severity of every possible adverse drug reaction. However, this information was provided more frequently in package inserts of Group C drugs than in other groups.

In addition, only 63.2% of the package inserts provided information on the possible influence of the medication on reaction time after using the medicine. Here the package

inserts of Group C also ranked significantly better than those for the other groups. However, only every second version with this information gave advice on the capability to drive a car or operate a machine.

51.2% of all analyzed package inserts included suitable measures for every adverse drug reaction. Only one of the 45 inserts for prescription-only medication gave an assessment on consumer benefit as compared with possible side effects.

Storage

Only 33.8% gave instructions on correct storage and 41.2% included no instructions on the appropriate storage temperature. Versions in Group C were significantly better in these two categories compared to the other groups.

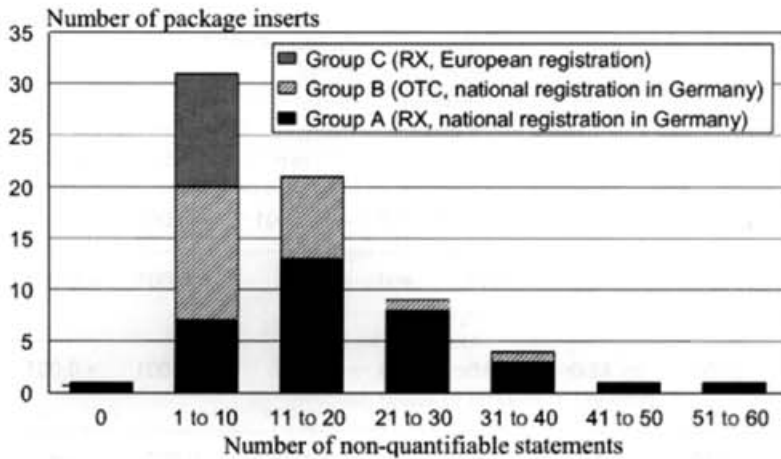


Figure 1. Number of non-quantifiable statements in package inserts (n = 68).

Every fifth package insert (20.0%) for preparations available only on prescription recommended: "Do not give this medication to other persons". Group C package inserts were again significantly better regarding this quality criterion.

38.2% of cases examined did not have more than one manufacturer's address. 85.3% of all versions included a telephone number, 69.1% a fax number and only 2.9% an internet address.

Analysis of comprehensibility and readability

Although the Directive 2001/83/EC and German drug law (AMG § 11) demand easily legibility and clearly comprehensible package inserts [N.N. 1998, The European Parliament and the Council of the European Union 2001], all 68 package inserts included foreign words which are usually more difficult to understand. These words were used significantly more often in versions of Group A (Table 2).

98.5% of package inserts contained non-quantifiable statements [Fuchs 2004]. For example "high dosage" or "use for a long time". The use of these terms was significantly lower in Group C (Table 2, Figure 1).

97.1% of all cases had repetitions or abbreviations, 83.8% included advertising elements and 8.8% contradictory information. One package insert had 18 repetitions of dif-

ferent contents, which markedly increased the length of this version.

Every fifth package insert (22.0%) contained more than 2,000 words. These were 3–4 written leaflets (size 210 × 297 mm) with a font size of 8 pt. Versions of Group A appeared to have more words than the others. Package inserts with European approval (Group C) used the shortest sentences and the least number of words (Table 2).

A font size larger than 10 pt occurred in only one package insert. The average font size was 8 pt (Table 2).

Discussion

It is concluded from these results that patients will probably not fully understand any of the 68 package inserts under study and therefore will not be able to follow the instructions to their best possible benefit. It is most likely that this conclusion also applies to other package inserts on the German market.

Providing dosage instructions only in milligram of active substance is a well-known problem in drug safety. The survey PAINT (package insert test) showed that up to 90% of patients do not understand this type of dosage instruction [Fuchs et al. 2004].

Other sources of potential mistakes in comprehensibility are due to non-quantifiable statements as found in non-specific dosage instructions (e.g. take 2–4 tablets, 1–3 times daily) and qualitative statements on the frequency of side effects (e.g. rare or common) [Fuchs 2004].

Berry and colleagues [2002] showed that qualitative descriptions of adverse drug reactions led to gross overestimation of risk. Students at Reading University (n = 200) found that the qualitative term "very rare" occurred with a mean frequency of 4% (EU assigned frequency: < 0.01%).

The European Commission [1998] recommended a method for testing the comprehensibility and readability of package inserts. However, it is not obligatory to test every package insert. Additionally, an obligatory standard method for testing all versions is not available.

We recommend therefore that every package insert be examined with regard to non-quantifiable statements, foreign words, ab-

breviations and measures taken to ensure that they contain all the important information using a standardized set of quality criteria.

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More information about the analyzed package inserts are available by the authors.

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