

Problems Identified in the Package Leaflets of the Portuguese Non-Generic Medicines



Problemas Identificados nos Folhetos Informativos dos Medicamentos Não Genéricos Portugueses

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ABSTRACT

Introduction: All medicines for human use are marketed with a package leaflet. Every package leaflet must contain an initial list mentioning all sections of the document in accordance to the European template Quality Review of Documents, being not too extensive, i.e. comprising approximately 1500 words. The so-called mixed leaflets contain information about medicines with more than one strength/pharmaceutical form, and only exceptionally are authorized. In this context, the objectives of the present study comprised the identification of issues in all package leaflets of Portuguese non-generic medicines: 1. to confirm the presence of an initial list, 2. to quantify the number of mixed leaflets, and 3. to evaluate their length (in number of pages).

Material and Methods: Consultation of the leaflets, in a public database (Infomed), according to the classification of the National Prescribing Guide (1st trimester 2012). The data collected was subject to quality control and statistical analysis.

Results: Identification of 2729 package leaflets, representing 3080 medicines. A total of 2042 leaflets were evaluated, with 181 (8.9%) missing the initial list and 351 (17.2%) being mixed. The average number of pages was 6.9 (SD=2.6), the minimum = 2 and the maximum = 26.

Discussion: In some cases, readability and comprehension of some Portuguese leaflets might be compromised since: 1) some leaflets did not contain an initial list, 2) were classified as mixed leaflets, and/or 3) were classified as too extensive.

Conclusion: Regulatory authorities and marketing authorization holders might need to take into consideration these issues during the development and approval of package leaflets.

Keywords: Pamphlets; Drug Labeling; Portugal.

RESUMO

Introdução: Todos os medicamentos de uso humano são comercializados com um folheto informativo. Estes documentos devem ter uma lista inicial com a identificação de todas as secções, de acordo com o modelo europeu Quality Review of Documents e não serem muito extensos, i.e. com cerca de 1500 palavras. Apenas excepcionalmente são autorizados folhetos relativos a mais de uma dose e/ou forma farmacêutica (folhetos mistos). Neste contexto, os objectivos incluem a identificação de problemas nos folhetos informativos de todos os medicamentos não genéricos portugueses quanto à presença da lista inicial, à frequência de folhetos mistos e ao número de páginas.

Material e Métodos: Consulta dos folhetos na base pública Infomed de acordo com a classificação do Prontuário Terapêutico – 10 (1^o trimestre 2012). Os dados recolhidos foram sujeitos a controlo de qualidade e tratamento estatístico.

Resultados: Identificação de 2729 folhetos em 3080 especialidades farmacêuticas. Foram avaliados 2042 folhetos (687 não estavam disponíveis), em que 181 (8,9%) não apresentaram lista inicial e 351 (17,2%) eram mistos. O número médio de páginas foi 6,9 (DP = 2,6), o mínimo = 2 e o máximo = 26.

Discussão: A leitura e compreensão adequadas dos folhetos portugueses em alguns casos podem estar comprometidas, dado que 1) alguns dos folhetos analisados não continham a lista inicial necessária à adequada localização das informações, 2) foram detetados folhetos mistos e/ou 3) foram encontrados folhetos com uma extensão acima do desejável.

Conclusão: Os resultados deste estudo devem informar o processo de desenvolvimento e aprovação dos folhetos pelos titulares da autorização da introdução no mercado e pelas autoridades reguladoras.

Palavras-chave: Folhetos Informativos; Rotulagem de Medicamentos; Portugal.

INTRODUCTION

The inclusion of a package leaflet in the packaging of all medicinal products is obligatory in the European Union, unless all the required information is directly conveyed on the outer packaging (article 58 of the Directive 2001/83/EC).¹ The patient information leaflet (PIL) should be designed according to the information included in the Summary of Product Characteristics (SPC), a document containing information aimed at health professionals (article 59 of the Directive 2001/83/EC, transposed at national level to Decree-Law nº 176/2006 (article 106)).²

Package leaflets of medicinal products must comply with certain characteristics, such as: 1) ease of understanding, facilitating localization of drug characteristics and understanding of its content, 2) efficiency, allowing for quick and successful consultation and 3) usefulness for the lay users.³ In addition to clarity and simplicity, its readability is also related to graphic and typographic aspects of the text, such as organization of headings and document navigability.^{4,5}

The structure of package leaflets is defined according to

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the QRD - Quality Review of Documents European model⁶ and with the exception of QRD's versions 1 and 2 (from 1996/97), every subsequent version includes an initial table of contents of all the main sections of the document. According to QRD's last version (n° 9, 2013), this table must comply with the following:

1. What X is and what it is used for;
2. What the patient should know before <taking it> <use it>;
3. How to <take it> <use it>;
4. Possible side effects;
5. Storage conditions;
6. Package contents and further information.^{6,7}

The table of contents is particularly useful for the patient, as it is known that package leaflets are often selectively read by patients, i.e. patients only look for information regarding a certain issue (such as dosage).⁸ The so-called combined or mixed package leaflets, regarding more than one pharmaceutical strength or form, are only allowed in exceptional or duly justified cases, in order to ensure the leaflet's simplicity. In these, clarity and simplicity of information regarding dosage and method of administration is crucial.⁹

According to the results of a cross-over study carried out in Jena's region (Germany) involving 1,105 participants in a 1st and 1,057 in a second phase project, questionnaires were applied to evaluate the perception of the information included in original as well as in modified or simplified package leaflets for five different drugs (enalapril, ibuprofen, paracetamol, repaglinide and telmisartan). The following requirements were considered in order to change the leaflets: 1) presentation of the information in a more concise format, 2) preferred font size: 11 pt, 3) contrasting background colours, 4) utilization of coloured titles in bold, 5) dosage expression as number of tablets or as exact volume, 6) avoidance of foreign words, 7) shorter sentences, 8) reducing expressions non-related to an exact quantification (as in "high dosages"), 9) avoiding abbreviations and repetitions. We obtained 92.6-94.4% correct responses with the modified/simplified version in comparison to only 74.7-85.8% with the original package leaflets. The dosage presentation was among the major issues identified in the original texts, which should be short and precise, preferably with the administration instructions quantified in terms of number of units or volume.¹⁰ Another study involving 452 participants attending 17 German community pharmacies found that 192 (42.5%) participants referred to difficulties in reading the package leaflets and 96 (21.3%) referred to some difficulties in understanding drug dosage.¹¹ Another survey on package leaflets, carried out in Germany and involving 1,900 people, found that most responders 1) read the documents, 2) ranked these as lengthy, 3) considered the information as unhelpful (one in five qualified it as unintelligible), and 4) 28% had already stopped taking the medication on at least one occasion due to misunderstanding of the content of the package leaflet.¹²

Lengthy package leaflets are known to add a layer of difficulty to patient understanding.¹²⁻¹⁶ Research involving 271 package leaflets of medicines available to the German market found that the information provided by more recently approved leaflets increased in terms of the amount of text, particularly regarding technical information.¹³ The tendency towards increasing the content in package leaflets was also confirmed in a review study on the changes over time regarding the QRD model.⁶ A controlled study involving 192 participants compared 3 package leaflets organized according to the German version of the QRD model (normal version) vs. the reduced/simplified version, i.e. specifically developed for the study. A questionnaire was applied in order to assess package leaflet's understanding and the shorter models were shown to be more adequate, with a better understanding in 15.7% of the cases and a 18.1% ($p < 0.05$) reduction in the time taken to locate the information in the text.¹⁴

Our study aimed to identify and confirm the presence of a table of contents, to quantify the mixed package leaflets likely to contain more complex dosage information and to assess the amount of text in leaflets (in number of pages), considering as relevant the potential impact of some of the general information in the leaflet on the adequate use of non-generic Portuguese drugs. In addition, the amount of text in lengthier leaflets assessed in this study was compared to the amount of text in at least one leaflet of a drug with the same formulation and pharmaceutical form, approved by a non-European Agency, also available for consultation in a public database and in which the same aspects were included.

MATERIAL AND METHODS

Our study followed a descriptive and cross-over design, carried out on the first trimester of 2012, based on the leaflets that were published in the *Infomed* database.¹⁷ A search for different non-generic drugs was carried out in this database, according to the classification of the Portuguese prescribing compendium (*Prontuário Terapêutico - 10*).¹⁸ *Infomed* is a public open-access database managed by the Portuguese medicines authority (*INFARMED - Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.*) and includes information on all medicinal products in the Portuguese market, namely their package leaflets.

The leaflets regarding hospital medicinal products were excluded from the study as most of these are to be administered under a health's professional direct intervention. Our study did not assess any leaflet regarding medicinal products ranked as generic, as these have a similar structure as non-generic medicines. In addition our study did not concern any case when an arbitration procedure regarding the reference medicine was expected to be in accordance with article 30 (2) of the Directive 2001/83/EC¹, upon which the harmonised text regarding the summary of product's characteristics and package leaflet will be published. All leaflets regarding drugs classified as generic or as exclusive for hospital administration, in

accordance with the classification system of this database (including branded generic medicines), were excluded from the study.

All leaflets regarding non-generic medicines identified in the *Infomed* database were characterised according to the following variables: presence of a table of contents (vs. absence), mixed (combined) package leaflets (vs. single) and number of pages per leaflet, according to the layout of the documents published in the database. In addition, they were classified according to a group of variables associated to the available classification in the *Infomed* database and in the *Prontuário Terapêutico – 10*.¹⁸ chemical composition, therapeutic group, medicine status (prescription-only [POM] vs. over-the-counter [OTC] medicines), type of approval (with vs. without centralised European Medicines Agency – EMA approval) and route of administration (oral, parenteral or dermal.). Although the centrally approved leaflets are not directly accessible in the *Infomed* database, this provides a link to EMA's site, where these leaflets are available for public online access.

All the variables were organized into a Microsoft Excel file and subject to quality control using the principles established in the NBR 5425 regulatory standard¹⁹ with randomization and re-analysis of approximately 10% of the identified leaflets. According to the quality control methodological principles no errors were detected. These pre-defined principles establish that the identification of more than one error by variable would involve re-assessing all the identified leaflets, as well as a second analysis, which proved unnecessary in our study.

At the same time, the number of words in the lengthier leaflets (herewith described as outliers or leaflets containing a number of pages considered as excessive when exceeding three times the interquartile range) were compared to the number of pages and words in at least one leaflet associated to a drug with similar pharmaceutical composition and form, available in the Australian public medicines agency (Therapeutic Goods Administration – TGA).²⁰ The number of words was quantified using the MS Word software, with the Word Count tool. The comparison of the number of words (instead of the number of pages) allows for a more precise analysis, especially due to the fact that the Australian package leaflets are published in three-column formatted documents, making a direct comparison more difficult. The leaflets in this database were selected as comparators as they are available online (unlike in the United States, where not every medicine has its leaflet available)²¹ and because they are approved by an extra-European medicine agency, i.e. following regulation principles not exactly overlapping but still similar to the European package leaflets.²⁰

The SPSS for Windows (version 19.0, IBM-SPSS, Chicago, IL) software was used for statistical analysis, involving the determination of the parameters of descriptive statistics as well as the statistical differences between groups of leaflets ranked by pages (2 to 5, 6 to 10 and more than 10 pages), with a $p < 0.05$ significance level. The intervals regarding the number of pages were based on the

analysis of the distribution of their frequencies.

RESULTS

Identified, selected and excluded leaflets

From a total of 2,729 (100%) package leaflets associated to non-generic medicines and covering 3,080 medicinal products, 2,042 (74.8%) were selected for evaluation, as 687 (25.2%) were not available in the *Infomed* database.¹⁷ None of these 687 leaflets is associated to any of the Portuguese top-seller 100 International Non-proprietary Names²² or to any centrally approved medicine. A total of 115 leaflets associated to hospital medicines were excluded from the study.

Leaflets with (vs. without) initial table of contents

As regards the 2,042 evaluated leaflets, 181 (8.9%) did not include a table of contents. We should mention that no centrally approved leaflet was found without a table of contents.

The distribution of leaflets with initial table of contents (1,861) by the different medicinal products is shown in Table 1. The medicines described in these leaflets were mainly given orally, parenterally or directly to the skin (dermal route) (59.2%, 15.8% and 11.1% from 1,861 leaflets, respectively).

The leaflets without table of contents regarded mostly medicines used in pathologies of 1) central nervous system, 22%, 2) gastrointestinal system, 19.9% and 3) musculoskeletal system, 15.5% (40, 36 and 28 from 181 leaflets, respectively).

Mixed (combined) leaflets

In total, 354 (100%) mixed leaflets were identified, from which 351 (99.1%) included an initial table of contents and 3 (0.1%) did not. The distribution of the mixed leaflets according to the medicine's status and the type of approval is shown in Table 2.

In the mixed leaflets with table of contents, 1) angiotensin-converting enzyme inhibitors, 7.4%, 2) antidepressants, 7.1%, and 3) antipsychotic, 4.8% (26, 25 and 17 from 351 leaflets, respectively) were the medicinal product groups most frequently found.

Leaflet's amount of text

As regards the distribution of the number of pages on the leaflets with vs. without initial table of contents regarding prescription-only vs. OTC medicines, with centralised approval or any other type of approval, the descriptive statistics parameters and statistical differences are shown in Table 3. According to the p -values shown in this Table, a higher percentage of lengthier leaflets were found, statistically significant in the group of leaflets with initial table of contents regarding prescription-only or centralised approved medicines.

In addition to the data shown in Table 3, we found that in the case of leaflets associated to POM, 75.5% (278 in 368) had less than 6 pages, while 63.6% of the leaflets associated to OTC medicines (950 from 1,493) had 6 to

Table 1 - Distribution of package leaflets by the different therapeutic groups

| Therapeutic Group in the Portuguese Prescribing Guide | Available leaflets* (n) | Available leaflets† (%) | Unavailable leaflets† (%) |
|---|-------------------------|-------------------------|---------------------------|
| G1: Infections | 163 | 74.4 | 25.6 |
| G2: Central Nervous System | 309 | 73.0 | 27.0 |
| G3: Cardiovascular System | 179 | 80.6 | 19.4 |
| G4: Blood | 59 | 66.3 | 33.7 |
| G5: Respiratory System | 123 | 76.9 | 23.1 |
| G6: Gastrointestinal System | 176 | 61.5 | 38.5 |
| G7: Genito-urinary System | 69 | 81.2 | 18.8 |
| G8: Hormones | 167 | 85.2 | 14.8 |
| G9: Musculoskeletal System | 162 | 87.1 | 12.9 |
| G10: Allergy | 39 | 92.9 | 7.1 |
| G11: Nutrition | 30 | 47.6 | 52.4 |
| G12: Volume replacement | 26 | 36.1 | 63.9 |
| G13: Skin disorders | 143 | 58.1 | 41.9 |
| G14: E&T disorders | 25 | 80.6 | 19.4 |
| G15: Eye disorders | 87 | 80.6 | 19.4 |
| G16: Oncology | 65 | 85.5 | 14.5 |
| G17: Poisoning | 1 | 33.3 | 66.7 |
| G18: Vaccines | 37 | 92.5 | 7.5 |
| G19: Diagnostics | 1 | 100.0 | 0.0 |
| Total | 1861 | | |

n: number of leaflets.

* Number of available leaflets with table of contents; † % of available vs. unavailable leaflets in the *Infomed* public database.¹⁶

10 pages. We found some medicine's leaflets with more than 10 pages: 0.8% associated to POM and 10.8% to OTC medicines.

Hormones and drugs used in treatment of endocrine pathology were those with lengthier leaflets (average = 9.5 pages; SD = 3.2) together with immune modulator drugs and antineoplastic drugs (average = 8.5 pages; SD = 3.1). The medicinal products group used in dermal pathology had the shortest leaflets (average = 4.6; SD = 1.5).

Comparison with leaflets from abroad

Shorter leaflets than Portuguese leaflets ranked as extreme outliers were found in the Australian TGA database²⁰, within the group of selected leaflets used for the comparative study (Table 4).

DISCUSSION

Assessed leaflets

Our sample of 2,042 leaflets was considered as

appropriate to our study as the leaflets of every non-generic drug described in the *Prontuário Terapêutico – 10*¹⁸ was identified at the *Infomed* database,¹⁷ even considering that some of these were not available in this database.

Leaflets with vs. without initial table of contents

The fact that some leaflets with no initial table of contents exist, i.e. without an initial description of every chapter on the leaflet, suggests that there are still leaflets designed according to expired QRD models in the public database, although the presentation of such a table was recommended from the third version of the QRD model onwards (1998).⁶ It may prove to be more difficult for the patients to locate the information in these leaflets therefore inducing less efficient reading. Considering that the patients often only look for specific information on the package leaflets, such as those regarding dosage or adverse reactions,²³ the lack of navigability of the documents may affect an efficient search for the required information.

Table 2 - Distribution of mixed (combined) leaflets

| | Total (n)* | Total (%) | Non-Mixed (n) | Mixed (n) | Ratio† |
|--------------------------|------------|-----------|---------------|-----------|--------|
| Medicine's status | | | | | |
| POM | 1493 | 80.2 | 1166 | 327 | 3.6 |
| OTC | 368 | 19.8 | 344 | 24 | 14.3 |
| Total | 1861 | 100 | 1510 | 351 | |
| Type of approval | | | | | |
| Centralised | 178 | 9.6 | 158 | 20 | 7.9 |
| Other | 1683 | 90.4 | 1352 | 331 | 4.1 |
| Total | 1861 | 100 | 1510 | 351 | |

n: number of leaflets with table of contents; POM: prescription-only medicines; OTC: over-the-counter medicines.

* Total = Mixed + Non-mixed; † Number of non-mixed leaflets divided by the number of mixed leaflets.

Table 3 - Distribution of the number of pages in leaflets

| | Number of pages | | | | | | Pearson Chi-square | p |
|--------------------------|-----------------|------|---------|--------------------|---------|---------|--------------------|---------|
| | Total (n) | % | Average | Standard deviation | Minimum | Maximum | | |
| Table of contents | | | | | | | | |
| Without | 181 | 8.9 | 4.9 | 2 | 2 | 15 | 60.6 | < 0.001 |
| With | 1861 | 91.1 | 6.9 | 2 | 2 | 26 | | |
| Total | 2042 | 100 | | | | | | |
| Medicine's status | | | | | | | | |
| POM | 1493 | 80.2 | 7.3 | 2.6 | 2 | 26 | 325.4 | < 0.001 |
| OTC | 368 | 19.8 | 4.9 | 1.5 | 3 | 12 | | |
| Total | 1861 | 100 | | | | | | |
| Type of approval | | | | | | | | |
| Centralised | 178 | 9.6 | 8.3 | 2.6 | 4 | 17 | 67.3 | < 0.001 |
| Other | 1683 | 90.4 | 6.7 | 2.6 | 2 | 26 | | |
| Total | 1861 | 100 | | | | | | |

n: number of leaflets; POM: prescription-only medicines; OTC: over-the-counter medicines.

Mixed (combined) leaflets

The mixed leaflets identified in our study concern the description of information on medicines with more than a single dosage or pharmaceutical form in the same leaflet.⁹ Among other issues, the information regarding dosage or administration form should be more difficult to look for due to the presence of competing facts. In these cases, the reader has to distinguish the different information available on the leaflet i.e. the reader has to specifically identify the dosage and/or the pharmaceutical form that best apply to his treatment.

We should mention that although dosage is a particularly important aspect for an adequate drug administration and is considered by patients as a major item,²⁴ the issues regarding an adequate presentation are not uncommon.^{10,11} Furthermore, the higher percentage of mixed leaflets is found in the top-selling group of medicinal products, such

as leaflets regarding drugs used in the central nervous system and the musculoskeletal system,²² suggesting an intense use and reading of mixed leaflets.

Unlike what would be expected, the national regulation²⁵ does not include any additional recommendation regarding the approval of mixed leaflets,⁹ although the EMA guidelines are followed in Portugal, as in the remaining countries of the European Union. Apparently, the EMA uses more selective mechanisms for the approval of mixed leaflets, considering that a much lower percentage of this type of leaflets has been detected in medicines with centralised approval.

Amount of text in leaflets

Some lengthy leaflets were found (outliers). This does not improve reading and understanding of leaflets by patients, according to different studies^{6,12-16}.

In addition, it has been estimated that the leaflets

Table 4 - Comparison of the Portuguese package leaflets considered as outliers vs. leaflets approved by the Australian Agency

| Composition | | Pharmaceutical Form | Number of words * | | Reduction rate † | Name of the Australian medicine |
|------------------|-------|-----------------------------------|--------------------|--------------------|------------------|---------------------------------|
| | | | Portuguese Leaflet | Australian Leaflet | | |
| Botulinum type A | Toxin | Powder for solution for injection | 7263 | 4053 | 55.8% | Botox |
| Somatropin | | Powder for solution for injection | 3710 | 1653 | 55.4% | SCITROPIN A 5mg/1.5mL |
| Risperidone | | Powder for solution for injection | 5559 | 2551 | 45.8% | Risperdal |
| Etonogestrel | | Implant | 6662 | 4289 | 35.0% | Implanon |
| Levonorgestrel | | Intrauterine device | 4832 | 3331 | 31.0% | Mirena |

* The number of words was quantified according to the documents published in the websites of the Portuguese and Australian Medicines Regulation Agencies^{17,20}

† The reduction rate was quantified according to the reduction on the number of words.

included in our study contained on average approximately 2,800 words, considering that 1) the average number of pages of the assessed leaflets was approximately seven and two) one standard A4 sheet written in serifed font size-11 includes about 400 words. The estimated value of the number of words is questionable as the documents available in the *Infomed* database are not exactly homogeneous regarding format, i.e. they show slight variations in sizes, fonts, margins and line spacing (non-standardized documents). According to another study by the authors, in a sub-sample of 531 randomized leaflets from all the leaflets selected to the present study 1) there was a 1,860 word average (± 860), 2) 195 leaflets (37%) included more than 2,000 words and 3) 105 (20%) leaflets had more than 2,500 words.

As such, the authors quantified the number of words in a small set of leaflets associated to centralised approved medicines in the German and in the Portuguese markets and published in EMA's site, in order to build an indicator regarding the variations in the number of words due to differences in language. This assessment confirmed that the Portuguese and German leaflets had a similar number of words, with only just 5% more words in the case of Portuguese leaflets, i.e. even considering the variations due to the language, some of the Portuguese leaflets are apparently too lengthy.

We should mention that the level of education may have a strong impact on the way patients from each country use leaflets. In the case of the Portuguese population, it is known that 44% has basic schooling levels, a higher percentage than in German population (3% of the population).²⁶ Therefore, it would be expected that lengthy leaflets have an even stronger impact on understanding and adequate use in the Portuguese population. In contrast, we also should mention that, although shorter leaflet production is recommended, i.e. with less than 1,500 words,¹⁵ it cannot be expected that all the leaflets would have this amount of text, as this rather depends on the relevant information for each medicine and substance.

Shorter leaflets without initial table of contents may be

explained by their structure having been built according to older and shorter QRD models,⁶ i.e. applied to the insertion of less information, when compared to more recent QRD models.^{6,7} In addition, the fact that OTC leaflets are significantly lengthier than those regarding POM may be explained by the higher technical complexity of the information that is needed to be included in POM's leaflets.²⁵ The fact that leaflets regarding centralised approved medicines are significantly shorter when compared to those without this type of approval may be also explained by the higher technical complexity of the information that is needed to be included in these medicines, such as with the new antineoplastic agents or the new drugs for diabetes.²

Comparison to leaflets in other countries

Leaflets regarding medicines with the same composition and pharmaceutical form were found in the TGA database²⁰ with approximately half of the words of leaflets ranked as extreme outliers. This reinforces the view that at least some of the Portuguese leaflets could be shorter. Even considering that a shorter number of words would be expected (approximately 6%) in leaflets written in English, when compared to the Portuguese translations of the same leaflet (value also based in the analysis of a small sample of leaflets published in the EMA's site written in English and compared to the version in Portuguese published in the same site), we think that inter-language variations do not explain the excessive length of leaflets ranked as extreme outliers.

Final considerations

Simplicity and clarity of written information are crucial in order to allow for readability of medicines' leaflets.^{5,27,28} Therefore, we consider that our study assessed relevant parameters to ensure simplicity, clarity and efficacy of the information in leaflets. Considering that there are no other similar studies published in Portugal, our study may correspond to a first contribution to improve Portuguese leaflet readability.

Globally, the issues found in package leaflets reinforce

the importance of the information given to patients by health professionals. In this fashion, patients have an opportunity to clarify their doubts and to receive information considered as crucial for the rational and safe use of medicines.²⁹⁻³¹ In addition, research on adequacy of presentation and amount of text in package leaflets, as well as the assessment of the impact of the use of mixed (combined) leaflets in health outcomes, should include specific readability tests aimed to assess response variations between patients or potential drug users in the different countries of the European Union, as there is heterogeneity in educational levels among these populations.²⁶

Although this was not the major focus of the present study, we found that some leaflets were not available in the *Infomed* database, which may eventually compromise the immediate access to the information by users (patients and health professionals), even considering that the latter preferably read the summary of product characteristics, which is also published in this database. This situation may be explained due to temporary regular updates. However, we should mention that on the first trimester of 2014 an average number of 265,000 visits to the website of the INFARMED (Study Topic/*Tráfego de visitas ao sítio* <http://www.infarmed.pt>. Unpublished raw data, 2014) confirms the importance of online information, even though the number of searches by health professionals only vs. other users is not known. There are several links in *Infomed's* website to non-accessible leaflets.

As regards leaflets associated to centralised approved medicines, no unavailable leaflets were found, showing the reliable online publication of these leaflets by the EMA. We should also mention the fact that these leaflets are not directly available in *Infomed's* database, i.e. there is a re-routing from *Infomed's* website to the EMA's website, consequently increasing the level of difficulty for some users as, despite leaflets being available in Portuguese, the information in the EMA's website is written in English.

Study limitations

Although approximately 80% of all leaflets regarding non-generic medicines were included in the Portuguese *Prontuário Terapêutico – 10*,¹⁸ the exact number of medicines absent from the list was not determined. Therefore, the number of non-generic medicine's leaflets that were not analysed is not known. The fact that the leaflets associated to hospital drugs were not included in the study may also be considered as a limitation as although most of these medicines are to be administered by health professionals, in some cases these may also be used by patients. Finally, the amount of text in leaflets was assessed by the number of pages of the official documents published online, instead of the real leaflets, which does not allow for an estimation of the real extension of the information in the original package leaflets.

CONCLUSION

Our study found that some leaflets do not include an initial table of contents, do not show separate sections regarding pharmaceutical strength or form, or are too lengthy. Reading and understanding of some leaflets regarding Portuguese medicines may be eventually compromised. The issues identified in this study should be taken into consideration in the future by marketing authorisation holders and by regulation authorities during the development and approval of leaflets associated to Portuguese medicines.

CONFLICT OF INTERESTS

The authors declare that they do not have any conflict of interests in writing this manuscript.

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