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ORIGINAL ARTICLE

Readability Assessment of Package Inserts of Biological Medicinal Products from the European Medicines Agency Website

Mª. Ángeles Piñero-López · Pilar Modamio · Cecilia F. Lastra · Eduardo L. Mariño

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Abstract

Background Package inserts that accompany medicines are a common source of information aimed at patients and should match patient abilities in terms of readability.

Objective Our objective was to determine the degree of readability of the package inserts for biological medicinal products commercially available in 2007 and compare them with the readability of the same package inserts in 2010.

Methods A total of 33 package inserts were selected and classified into five groups according to the type of medicine: monoclonal antibody-based products, cytokines, therapeutic enzymes, recombinant blood factors and other blood-related products, and recombinant hormones. The package inserts were downloaded from the European Medicines Agency website in 2007 and 2010. Readability was evaluated for the entire text of five of the six sections of the package inserts and for the 'Annex' when there was one. Three readability formulas were used: SMOG (Simple Measure of Gobbledygook) grade, Flesh-Kincaid grade level, and Szigriszt's perspicuity index.

Results No significant differences were found between the readability results for the 2007 package inserts and those from 2010 according to any of the three readability indices studied ($p > 0.05$). However, there were significant differences ($p < 0.05$) between the readability scores of the sections of the package inserts in both 2007 and 2010. The readability of the package inserts was above the recommended sixth grade reading level (ages 11–12) and may lead to difficulties of understanding for people with limited literacy.

Conclusions All the sections should be easy to read and, therefore, the readability of the medicine package inserts studied should be improved.

Key Points

The readability of the package inserts for biological medicinal products available on the European Medicines Agency website assessed is above the sixth grade reading level and may therefore lead to difficulties of understanding for people with limited literacy skills

No substantial improvement was observed from 2007 to 2010 in the readability scores (SMOG, Flesch-Kincaid, and Szigriszt) of the package inserts studied

The order from the easiest to read (greatest readability) to the least easy to read (lowest readability) of the sections was: "5. How to store X" > "Annex" > "3. How to take X" > "2. What you need to know before you take X" > "1. What X is and what it is used for" > "4. Possible side effects"

Mª. Á. Piñero-López · P. Modamio · C. F. Lastra · E. L. Mariño (✉)
Clinical Pharmacy and Pharmacotherapy Unit, Department of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, University of Barcelona, Av. Joan XXIII s/n, 08028 Barcelona, Spain
e-mail: emarino@ub.edu

1 Introduction

Biological medicinal products are becoming an increasingly important part of the treatment arsenal, bringing

novel and life-saving therapies to patients with some of the most difficult diseases to treat [1, 2]. In the EU, it is obligatory to assess requests to authorise medicines derived from biotechnology processes via a centralised procedure. This means that a single marketing authorisation awarded by the European Commission is valid in all the EU countries. Furthermore, the European Medicines Agency (EMA) publishes the product information that includes, among other information, the package inserts for all authorised presentations of every medicine granted a central marketing authorisation and provides them in all EU languages [3, 4].

The package inserts that accompany medicines contain information that is very important for the patient, as they provide information on all the important aspects of the medicine, including how to take or use it correctly and safely, as well as how to understand the relation between the risks and benefits of using it. Therefore, they are frequently used by patients, in addition to healthcare professionals, as a source of information relating to medicines [5].

Since 2005, European legislation requires manufacturers to perform consultations with target patient groups (user testing) to ensure that information leaflets are legible, clear and easy to use. Moreover, the European Commission publishes updated guidelines that explain how to write package inserts well in order to increase their readability [6]. The *Guideline on the Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use* was published in accordance with Article 65(c) of Directive 2001/83/EC to provide guidance on how to ensure that the information on the label and in the package leaflet is accessible to and can be understood by those who receive it [6]. This guidance, published in January 2009, recommended in point 5 ('Syntax') the following: "… Aim to use simple words of few syllables. Long sentences should not be used. It is better to use a couple of sentences rather than one longer sentence, especially for new information …" The corresponding variables of word length and sentence length are used in the readability formulas to predict the comprehension difficulty of written materials. Different studies [7–9] support the value of readability indices as surrogate measures of how well written documents address different levels of health literacy, and indicate that they could generate results that match the experience of real patients.

Numerous studies assess the grade reading level of package inserts and information on medicines in general, together with that of other written material related to healthcare and aimed at patients, much of which is available online. However, many of the studies have shown that the grade reading level of the materials is higher than the average reading level of the target population [10–14]. This situation represents a problem that not only affects the text itself but also has an effect on general health literacy [15]. Given this situation, the US National Institutes of Health recommend that material written for end users such as patients should not have a readability above that corresponding to the sixth or seventh grade level (ages 11–13) [16], since low health literacy is related to poorer health outcomes and poorer use of healthcare services [17]. In view of these findings, in conjunction with the ever greater use of biological medicinal products that will have an increasing impact on healthcare in the future, it seems to be important to know whether the package inserts that accompany such medicines have limitations related to readability. It is also important to know this at the level of the sections that go to make up the package insert, since each patient may have different interests, worries or needs related to the information. To our knowledge, the adequacy and suitability of package inserts that are available online for these drugs has not been tested over time after trading authorisation. Therefore, the main objective of the current study was to determine the degree of readability of package inserts for biological products that were commercially available in 2007 and compare it with the readability of the package inserts for the same medicines that were still commercially available in 2010. We might expect changes between those 2 years, specifically, some improvement in package inserts should be observed, taking into account that the guideline mentioned above was published between these years.

2 Methods

2.1 Package Inserts for Biological Products Included

The sample that we studied consisted of 33 package inserts for biological products that were authorised by the EMA as of January 2007 and continued to be authorised in July 2010. They were divided into five groups depending on the source of the drug [18]: monoclonal antibody-based products, cytokines, therapeutic enzymes, recombinant blood factors and other blood-related products, and recombinant hormones (Table 1).

The package inserts were obtained from the EMA webpage [4]. The package inserts for the selected medicines were downloaded at two different times: in January 2007 and July 2010. The first study of the readability of package inserts took place in 2007, with an equivalent study in 2010, 1 year after the European Commission guideline on readability came into effect (June 2009). On both occasions, the same pharmaceutical presentation was used for each package insert. Each package insert was copied as plain text and saved as an individual Microsoft® Word® 2007 document.

Table 1 Biological medicinal products studied ($n = 33$)

Active substance	Date of authorisation	Therapeutic area
Monoclonal antibody-based products ($n = 6$)		
Sulesomab	14 Feb 1997	Osteomyelitis/radionuclide imaging
Rituximab	2 Jun 1998	Rheumatoid arthritis/chronic lymphocytic leukaemia/non-Hodgkin's lymphoma
Basiliximab	9 Oct 1998	Kidney transplantation
Infliximab	13 Aug 1999	Psoriatic arthritis/rheumatoid arthritis/ulcerative colitis/Crohn's disease/psoriasis/ankylosing spondylitis (Bechterew's disease)
Palivizumab	13 Aug 1999	Respiratory syncytial virus
Trastuzumab	28 Aug 2000	Breast neoplasms/stomach neoplasms
Cytokines ($n = 10$)		
Interferon beta-1b	30 Nov 1995	Multiple sclerosis
Interferon beta-1a	13 Mar 1997	Multiple sclerosis
Epoetin beta	16 Jul 1997	Renal anaemia/autologous blood transfusion/anaemia with related symptoms in adult cancer patients receiving chemotherapy
Interferon beta-1a	4 May 1998	Multiple sclerosis
Tasonermin	13 Apr 1999	Sarcoma
Etanercept	3 Feb 2000	Juvenile idiopathic arthritis/psoriatic arthritis/rheumatoid arthritis/psoriasis/Ankylosing spondylitis
Interferon alfa-2b	09 Mar 2000	Carcinoid tumour/chronic hepatitis B or C/hairy cell leukaemia/chronic myelogenous leukaemia/follicular lymphoma/melanoma/malignant multiple myeloma
Peginterferon alfa-2b	29 May 2000	Chronic hepatitis C
Darbepoetin alfa	08 Jun 2001	Renal anaemia/anaemia with related symptoms in adult cancer patients receiving chemotherapy
Pegfilgrastim	22 Aug 2002	Neutropenia/febrile neutropenia caused by the use of cytotoxic chemotherapy
Therapeutic enzymes ($n = 4$)		
Imiglucerase	17 Nov 1997	Gaucher disease
Rasburicase	23 Feb 2001	Hyperuricemia
Agalsidase alfa	03 Aug 2001	Fabry disease
Agalsidase beta	03 Aug 2001	Fabry disease
Recombinant blood factors and blood-related products ($n = 8$)		
Eptacog alfa (activated)	23 Feb 1996	Factor VII deficiency/haemophilia A/haemophilia B/Glanzmann's thrombasthenia
Reteplase	29 Aug 1996	Myocardial infarction
Desirudin	09 Jul 1997	Venous thrombosis
Nonacog alfa	27 Aug 1997	Haemophilia B
Moroctocog alfa	13 Apr 1999	Haemophilia A
Octocog alfa	04 Aug 2000	Haemophilia A
Octocog alfa	04 Aug 2000	Haemophilia A
Tenecteplase	23 Feb 2001	Myocardial infarction
Recombinant hormones ($n = 5$)		
Follitropin alfa	20 Oct 1995	Anovulation/hypogonadism/female infertility/assisted reproductive techniques
Thyrotropin alfa	09 Mar 2000	Thyroid neoplasms
Lutropin alfa	29 Nov 2000	Female infertility/ovulation induction
Somatropin	16 Feb 2001	Pituitary dwarfism/turner syndrome
Eptotermin alfa	17 May 2001	Tibial fractures

Readability was assessed over the whole text of five of the six sections that usually make up the package inserts: '1. What X is and what it is used for', '2. What you need to know before you take (or use) X', '3. How to take (or use) X', '4. Possible side effects' and '5. How to store X'. We excluded the section '6. Contents of the pack and other information' as it was very similar for all the products and because we considered it to be less relevant to patients. We

also evaluated the section 'Annex', which includes instructions for use, in the package inserts that included it ($n = 8$ package inserts in 2007 and $n = 9$ package inserts in 2010 included the section 'Annex'). The readability scores were compared between the 2 years when the package inserts were downloaded.

2.2 Readability Indices

The readability of the package inserts was measured using the following readability indices: the Simple Measure of Gobbledygook (SMOG) grade (SMOG), the Flesch-Kincaid grade level (FKGL) and Szigriszt's perspicuity index (PERS).

SMOG is recommended for use in healthcare literature because it is based on more recent criteria for determining reading grades than the other formulas [19] and it considers 100 % expected comprehension [19, 20], an important aspect in the context of healthcare. FKGL is one of the most commonly used readability formulas in healthcare literature published recently [19]. The third formula, Szigriszt's, was designed for Spanish, and it was used to analyse the results qualitatively, by describing the readability of the package inserts in terms of adjectives (very easy, easy, rather easy, standard, rather difficult, difficult and very difficult).

The SMOG formula uses the number of words of three or more syllables per sentence as a variable. Following the steps laid out by McLaughlin [20] using manual calculations instead of readability software, a numerical value called the SMOG grade was obtained, which estimates the level of education required to understand the text. In this way, it is understood that "SMOG 13–16 indicates the need for college education, 17–18 the need for graduate training, and 19 and above, the need for a higher professional qualification" [20]. The Flesch-Kincaid formula contains two variables: the number of words per sentence and the number of syllables per word [21]. To calculate it, we used the Microsoft® Word® 2007 word processing software working within the Microsoft® Windows® 7 operating system (Microsoft Corporation). From the 'Review' tab, the 'Show readability statistics' box in the 'Spelling and Grammar' section was checked, and English was selected as the language on the status bar. Once these selections are made, FKGL is automatically displayed in the Readability Statistics window after the spelling of the text has been checked. FKGL is a number that indicates the level of schooling required to understand the text. So, both SMOG and FKGL indicate the reading grade level or number of years of education required to understand the text, from which we can calculate the age required to understand the text.

PERS was obtained by applying the formula established by Szigriszt for text samples of any size written in Spanish [22]. Given that the variables needed to use the formula are the same as those for the Flesch-Kincaid formula, the number of words per sentence was retrieved from the "readability statistics" tool of Microsoft® Word® 2007 as explained above, and the number of syllables per word was obtained by extracting this variable from the formula that Microsoft® Word® 2007 uses to calculate FKGL. In this way, we used a spreadsheet to obtain the variables and apply the Szigriszt formula to the selected package inserts. The result was a numerical value called the level of ease of reading (PERS) that ranged from 0 to 100, and is interpreted as follows: very easy ($85 < \text{PERS} < 100$), easy ($75 < \text{PERS} < 85$), rather easy ($65 < \text{PERS} < 75$), standard ($50 < \text{PERS} < 65$), rather difficult ($35 < \text{PERS} < 50$), difficult ($15 < \text{PERS} < 35$) and very difficult ($0 < \text{PERS} < 15$).

The three formulas were applied in order to evaluate the readability of the sections in each package insert, for each year and using the whole text, despite the formulas offering the possibility of using samples of the texts, in order to avoid possible bias that could be introduced by using only a sample.

2.3 Statistical Analysis

The data were analysed using the statistical software package Deducer (R version 2.15.0). The Shapiro–Wilk test was used to check for the normality of data.

For each medicine and for each readability index, we obtained either five values (one for each section) or six if the package insert included an annex. In order to arrive at a single value for each package insert, we took the mean of all section values for each package insert. These 33 readability scores (one for each biological medicinal product) were used to study the possible differences between the readability of the package inserts from 2007 and those from 2010 and also to compare, within each year, the differences between the groups of medicines as a function of their source and date of authorisation. In these three comparative studies, the groups of scores followed a normal distribution, so we used parametric statistical tests: Student's *t*-test for the comparison between the 2 years of study and also to study differences between medicines as a function of their date of authorisation, and analysis of variance (ANOVA) to study differences between the types of medicine based on their source.

In contrast, to study possible differences between the sections of the package inserts, we used the values for each one of the sections (as well as repeating the analysis independently for each year). We established that the values for each section and year of study did not follow a normal distribution, and so we used the non-parametric Kruskal–Wallis test (we applied the Bonferroni correction

to perform a multiple-comparison between pairs of sections).

Pearson's correlation coefficient was used to assess the relationship between the three reading grade level formulas.

All the statistical tests used a 95 % confidence level, and a p value below 0.05 was considered significant.

3 Results

Table 2 shows the mean values, standard deviation (SD) and ranges of the three readability index scores calculated for each medicine and year ($n = 33$). Application of the t-test revealed no significant differences between the readability results of the package inserts in 2007 and those in 2010, according to any of the readability indices used ($p > 0.05$).

In the comparative analysis of the readability indices as a function of the source of the biological drugs, after ANOVA, no differences were detected between the means of the groups in either of the 2 years studied ($p > 0.05$) using SMOG and FKGL, but PERS showed a difference in 2010 ($p < 0.05$) between enzymes and cytokines, as revealed by the Bonferroni post-test for multiple comparisons.

For the comparative analysis of the readability indices as a function of the year of authorisation of the product, the medicines were divided into two groups: those that were authorised between 1995 and 1999 ($n = 17$); and those that were authorised between 2000 and 2002 ($n = 16$). The t-test revealed no differences between the group means in either of the years studied ($p > 0.05$).

With regard to the comparative study of the readability indices of the different sections that make up the package insert, Table 3 shows the medians, ranges and 95 % confidence intervals (CIs) of the three readability index scores calculated for each section and year studied. Figure 1 represents the descriptive statistics of the sections for each readability index and the 2 years studied. The Kruskal–Wallis test resulted in p values lower than 0.05 in all cases, so there were statistically significant differences between the readability scores of the six sections for each year of study. In addition, using the Bonferroni post-test for multiple comparisons (Table 4), in the majority of cases the differences were observed when the medians of the sections were compared pairwise ($p < 0.05$).

As for the relationship between the three reading level formulas used, a significant correlation was observed between the readability formulae applied: SMOG-FKGL $r = 0.9377$, 95 % CI 0.9236–0.9493; SMOG-PERS $r = -0.8642$, 95 % CI -0.8886 to -0.8349; FKGL-PERS $r = -0.9743$, 95 % CI -0.9791 to -0.9683.

4 Discussion

In terms of patient-centred safety, the role played by written information related to health in general and more specifically to medicines is considered to be an important way to complement and reinforce the verbal information offered by healthcare professionals [23].

The primary objective of this research was to determine the level of readability of package inserts available online for medicinal biological products (from the EMA website) in two different years (2007 and 2010).

This study shows that there was no substantial improvement in the readability of the package inserts studied between 2007 and 2010. This result does not match our expectations, since the European Commission guideline [6] recommended the use of simple words with few syllables, and avoidance of long sentences; taking these criteria into account, the readability of package inserts should have improved.

With respect to the comparison of the readability of the package inserts studied depending on the group the medicine belonged to in accordance with its source, no significant differences were observed in 2007 or in 2010. The same was true of the study of the correlation between the readability of the package inserts and the group to which the medicine belonged depending on its year of initial authorisation. Consequently, these two variables (source and date of authorisation) did not influence the readability of the package inserts.

Analysis of the readability of the sections confirmed statistically significant differences between the readability scores of the six sections for each year of study when pairwise comparisons of the sections for each year studied were performed, since significant differences in readability level were observed ($p < 0.05$) in most cases (Table 4). It is particularly noteworthy that no differences were observed between sections 1 and 2 in 2007, but differences were found in 2010 in all three indices. In addition, our results using FKGL and PERS were remarkably similar, while the SMOG values differed only slightly more.

Moreover, we observed that the median values for SMOG were between 14 (section 5) and 20 (section 4) in 2007, and between 14 (section 5) and 21 (section 4) in 2010 (Table 3). Similar, though slightly lower, values were obtained in all cases for FKGL. These data agreed with the PERS scores, in which the lowest values (most difficult to understand) corresponded to section 4 in both years, and the highest values (easiest to understand) to section 5. Thus, application of the three indices yielded consistent results, so that we could determine the following order of the readability of the sections of the package insert (from easiest to understand to most difficult) for both years studied: 'section 5' > 'Annex' > 'section 3' > 'section 2' > 'section 1' > 'section 4'.

Table 2 Descriptive statistics of the readability scores of package inserts assayed ($n = 33$)

	SMOG				FKGL				PERS			
	2007		2010		2007		2010		2007		2010	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Monoclonal antibodies-based products ($n = 6$)												
Sulesomab	16.2 (3.3)	11–20	16.4 (2.5)	13–20	16.8 (2.5)	13.3–19.5	16.5 (3.5)	10.9–19.9	52.3 (8.4)	44.2–62.1	55.5 (13.7)	44.0–77.7
Rituximab	16.2 (2.9)	12–20	17.4 (4.5)	13–25	14.9 (3.9)	8.4–19.0	16.9 (5.5)	10.5 –25.6	64.5 (15.8)	50.9–91.6	58.0 (18.4)	30.7–82.5
Basiliximab	17.0 (3.6)	12–22	17.2 (4.7)	11–24	16.1 (4.5)	9.9–22.2	15.9 (6.7)	5.4–24.0	59.2 (16.9)	36.5–83.0	62.0 (27.0)	33.7–106.8
Infliximab	17.8 (2.9)	16–23	17.6 (4.8)	14–26	17.7 (3.9)	14.3–23.9	16.9 (5.9)	11.2–26.6	51.6 (15.6)	29.7–66.5	56.2 (20.7)	27.1–80.7
Palivizumab	15.6 (2.5)	12–19	16.6 (3.3)	12–21	15.0 (3.2)	9.4–17.4	14.4 (3.5)	9.0–18.5	62.7 (13.7)	52.0–85.0	67.9 (15.9)	46.4–88.0
Trastuzumab	17.0 (3.4)	13–22	17.0 (3.7)	13–22	16.4 (4.5)	10.0–22.2	16.6 (4.6)	10.0 – 22.1	59.2 (17.0)	41.4–87.0	59.0 (17.5)	42.0–87.0
Cytokines ($n = 10$)												
Interferon beta-1b	17.5 (2.7)	13–21	17.7 (3.1)	14–23	16.6 (3.1)	12.0–21.3	16.4 (4.1)	11.4–23.4	57.0 (11.7)	39.0–72.7	58.7 (14.8)	35.9–77.1
Interferon beta-1a	17.6 (2.5)	14–20	15.5 (1.8)	14–18	16.3 (3.0)	12.3–18.8	14.1 (2.2)	11.7–17.0	58.1 (11.8)	45.7–73.1	64.8 (9.1)	52.0–75.5
Epoetin beta	16.6 (2.1)	15–20	16.4 (1.7)	15–19	15.7 (3.0)	12.8–20.4	15.3 (2.9)	11.9–19.5	59.3 (12.6)	40.6–71.7	61.3 (12.2)	44.1–75.9
Interferon beta-1a	16.2 (2.2)	14–19	16.4 (1.9)	14–19	15.5 (2.5)	12.1–17.8	15.2 (2.3)	12.5–17.9	60.2 (10.0)	50.7–73.9	61.5 (9.7)	51.2–73.1
Tasonermin	19.2 (2.5)	15–21	18.0 (3.8)	12–22	19.3 (2.8)	15.0–22.2	16.6 (4.6)	8.8–20.6	48.6 (8.9)	37.7–62.0	58.1 (20.1)	41.9–93.1
Etanercept	17.2 (2.8)	14–21	17.5 (2.7)	14–21	15.6 (3.5)	11.5–21.5	15.6 (3.5)	11.3–21.3	63.5 (13.7)	38.5–77.0	63.8 (13.3)	41.0–78.7
Interferon alfa-2b	17.7 (3.4)	14–22	17.8 (3.3)	14–23	15.9 (3.5)	11.2–19.5	15.9 (3.5)	11.7–20.1	61.7 (12.8)	49.1–79.7	61.7 (12.3)	48.9–77.0
Peginterferon alfa-2b	17.7 (4.5)	13–26	18.5 (5.0)	14–28	16.3 (3.7)	12.1–22.4	17.5 (5.3)	12.3–26.7	59.9 (10.7)	47.0–72.8	56.2 (15.2)	33.6–71.7
Darbepoetin alfa	16.5 (1.8)	14–19	16.3 (1.5)	14–18	15.3 (2.5)	12.0–17.9	15.3 (2.6)	12.1–17.8	61.0 (9.8)	51.1–74.7	61.2 (10.9)	49.8–75.0
Pegfilgrastim	15.5 (1.6)	14–18	16.2 (2.6)	14–20	14.3 (2.4)	11.7–17.2	15.0 (3.2)	11.5–19.4	65.0 (10.0)	52.6–77.1	63.8 (10.8)	51.5–76.7
Therapeutic enzymes ($n = 4$)												
Imiglucerase	18.2 (2.2)	15–20	18.0 (3.5)	14–23	17.6 (2.5)	14.0–19.4	17.9 (4.3)	12.3–23.2	53.0 (10.7)	43.4–69.6	52.1 (15.5)	36.7–74.5
Rasburicase	16.2 (1.9)	13–18	17.8 (3.4)	13–22	15.0 (3.6)	9.3–18.2	17.3 (4.9)	9.4–21.9	61.1 (16.1)	45.8–86.2	53.1 (19.5)	38.4–85.8
Agalsidase alfa	16.6 (3.5)	13–22	16.6 (3.5)	13–22	15.9 (4.3)	10.7–21.7	15.9 (4.4)	10.5–21.7	61.2 (14.9)	44.2–81.4	61.5 (15.2)	44.5–82.6
Agalsidase beta	18.4 (3.1)	15–23	18.0 (5.1)	13–26	18.4 (3.6)	13.5–22.8	18.3 (6.7)	10.8–27.4	51.4 (12.6)	35.7–70.7	51.8 (24.2)	20.5–81.4
Recombinant blood factors and blood-related products ($n = 8$)												
Eptacog alfa (activated)	15.0 (1.7)	12–17	16.0 (1.7)	15–19	14.4 (2.7)	10.5–18.1	15.3 (2.8)	12.1–19.8	64.1 (11.6)	47.1–79.8	62.7 (10.5)	48.9–76.3
Reteplase	17.4 (3.4)	13–22	17.4 (3.4)	13–22	16.5 (3.4)	11.8–20.7	16.6 (3.4)	11.8–20.7	58.0 (11.8)	44.3–75.7	57.7 (11.8)	44.3–75.7
Desirudin	16.6 (1.5)	15–18	17.6 (2.7)	14–21	15.0 (2.2)	11.5–17.6	16.4 (3.5)	11.8–19.0	62.7 (9.4)	50.7–76.7	58.2 (13.2)	43.5–75.3
Nonacog alfa	17.0 (1.4)	16–19	16.8 (1.6)	15–19	16.4 (2.0)	14.3–18.9	16.0 (2.5)	12.4–18.2	57.2 (8.8)	46.2–66.9	59.4 (11.6)	46.6–76.4
Moroctocog alfa	18.0 (3.5)	15–24	17.0 (2.4)	13–19	17.3 (4.0)	13.4–23.8	16.5 (2.3)	13.5–19.2	54.1 (14.9)	29.9–68.9	56.9 (9.8)	45.6–69.5
Octocog alfa	17.6 (2.9)	14–22	17.4 (2.3)	14–20	17.2 (2.6)	13.4–20.7	17.2 (2.3)	13.3–19.0	53.3 (7.6)	44.0–65.3	53.1 (7.6)	46.1–65.8
Octocog alfa	17.6 (2.9)	14–22	17.2 (2.4)	14–20	17.0 (2.7)	13.3–20.7	16.9 (2.4)	13.1–18.7	54.3 (8.0)	44.0–65.8	54.0 (8.2)	46.1–67.0
Tenecteplase	17.8 (2.8)	15–22	18.0 (3.2)	15–23	17.4 (2.9)	14.7–22.2	17.4 (3.2)	14.7–22.5	52.4 (11.1)	34.8–62.6	52.9 (12.7)	34.0–67.1

Table 2 continued

	SMOG				FKGL				PERS			
	2007		2010		2007		2010		2007		2010	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Recombinant hormones ($n = 5$)												
Follitropin alfa	17.8 (2.6)	14–21	17.8 (2.6)	14–21	17.0 (3.4)	12.3–21.3	17.0 (3.4)	12.3–21.3	55.6 (12.8)	38.8–72.0	55.6 (12.8)	38.8–72.0
Thyrotropin alfa	18.0 (3.6)	13–22	17.2 (3.0)	13–21	17.0 (4.4)	10.7–22.1	16.4 (3.8)	10.7–20.5	55.6 (16.6)	37.9–81.0	57.3 (15.5)	41.7–81.0
Lutropin alfa	17.8 (2.9)	14–21	18.0 (2.7)	14–21	16.2 (3.5)	12.2–21.4	16.4 (3.6)	12.3–21.4	59.3 (12.6)	39.9–73.3	58.1 (13.4)	39.9–72.9
Somatropin	17.0 (2.9)	13–21	17.0 (2.9)	13–21	16.3 (3.7)	10.6–20.7	16.3 (3.7)	10.6–20.7	57.0 (15.5)	39.9–81.4	57.0 (15.5)	39.9–81.4
Eptotermin alfa	18.6 (3.9)	14–24	18.6 (3.5)	14–23	18.2 (5.9)	11.1–26.3	18.2 (5.7)	10.8–25.5	52.3 (19.6)	29.3–79.6	53.8 (18.5)	34.5–81.2

SMOG Simple Measure Of Gobbledegook grade, *FKGL* Flesch-Kincaid grade level, *PERS* Szigriszt's perspicuity index, *SD* standard deviation

Table 3 Descriptive statistics of the readability scores by section of package inserts assayed

	2007						2010					
	Sec 1 ($n = 33$)	Sec 2 ($n = 33$)	Sec 3 ($n = 33$)	Sec 4 ($n = 33$)	Sec 5 ($n = 33$)	Annex ($n = 8$)	Sec 1 ($n = 33$)	Sec 2 ($n = 33$)	Sec 3 ($n = 33$)	Sec 4 ($n = 33$)	Sec 5 ($n = 33$)	Annex ($n = 9$)
SMOG												
Median	18	17	16	20	14	15	19	17	16	21	14	15
95 % CI	17.7–19.2	16.9–17.7	15.8–16.8	19.7–21.2	13.3–14.2	14.5–16.0	18.0–19.3	16.8–17.6	15.7–16.5	20.2–22.1	13.3–14.0	14.5–15.5
Range	15–24	14–19	14–21	17–26	11–16	14–17	15–23	14–20	14–20	17–28	11–15	14–16
FKGL												
Median	17.8	16.8	15.2	19.5	12.0	12.9	18.9	16.7	15.0	20.1	11.7	13.0
95 % CI	17.6–19.5	16.3–17.2	14.9–16.1	18.9–20.4	11.4–12.6	12.3–14.0	18.0–19.6	16.3–17.2	14.8–15.7	19.3–21.6	10.8–12.0	12.1–13.5
Range	15.0–26.3	13.9–18.9	13.3–20.9	16.4–23.9	8.4–15.0	11.8–14.9	15.0–25.5	13.8–19.0	13.0–18.4	13.7–27.4	5.4–14.7	11.5–14.2
PERS												
Median	51.1	56.5	62.4	46.7	73.9	72.0	46.8	55.9	62.4	45.6	76.4	72.0
95 % CI	45.9–52.0	53.4–56.8	58.7–63.2	44.0–49.5	71.9–77.4	67.7–74.3	45.5–50.7	53.3–56.8	60.2–64.1	41.4–49.3	75.1–81.0	69.7–74.6
Range	29.3–62.1	44.2–63.2	45.3–69.7	29.7–68.5	60.6–91.6	64.2–76.1	34.5–61.5	44.0–63.4	50.1–70.0	20.5–77.4	61.0–106.8	66.9–76.7

SMOG Simple Measure Of Gobbledegook grade, *FKGL* Flesh-Kincaid Grade Level, *PERS* Szigriszt's perspicuity index, *Sec* package insert sections, *Sec 1* What X is and what it is used for, *Sec 2* What you need to know before you take (or use) X, *Sec 3* How to take (or use) X, *Sec 4* Possible side effects, *Sec 5* How to store X, *CI* confidence interval

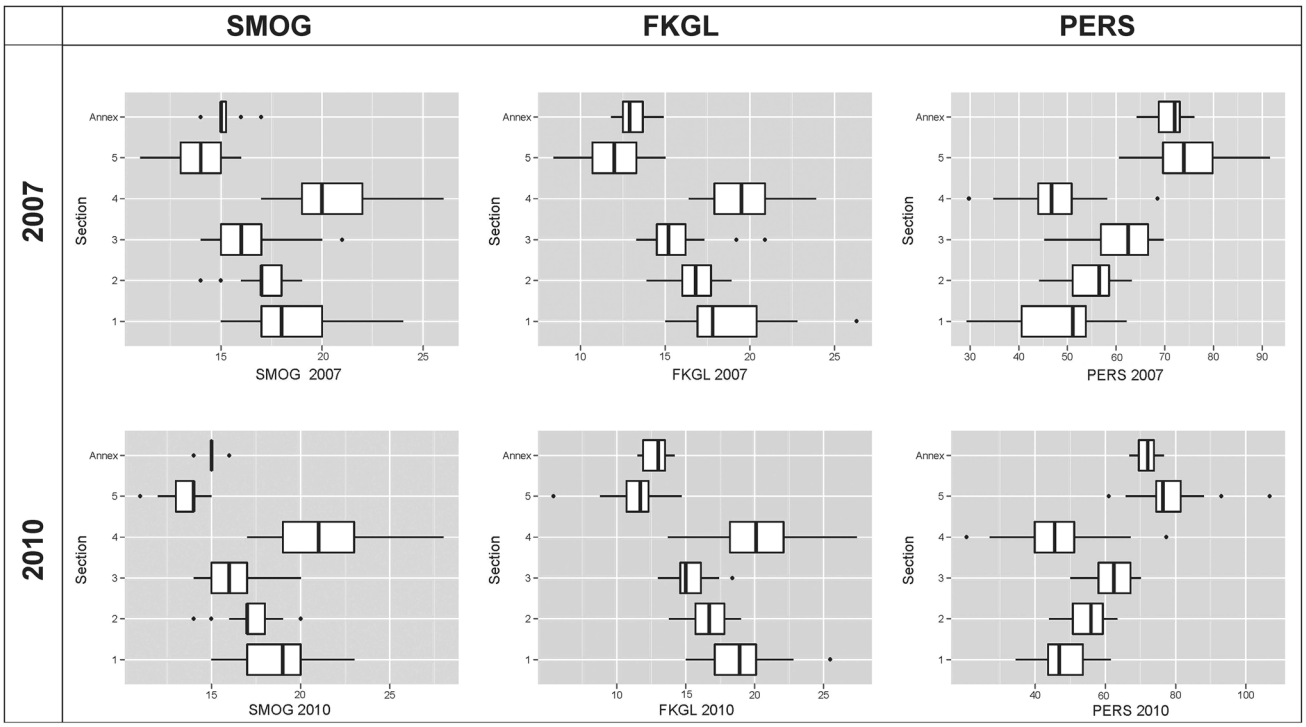


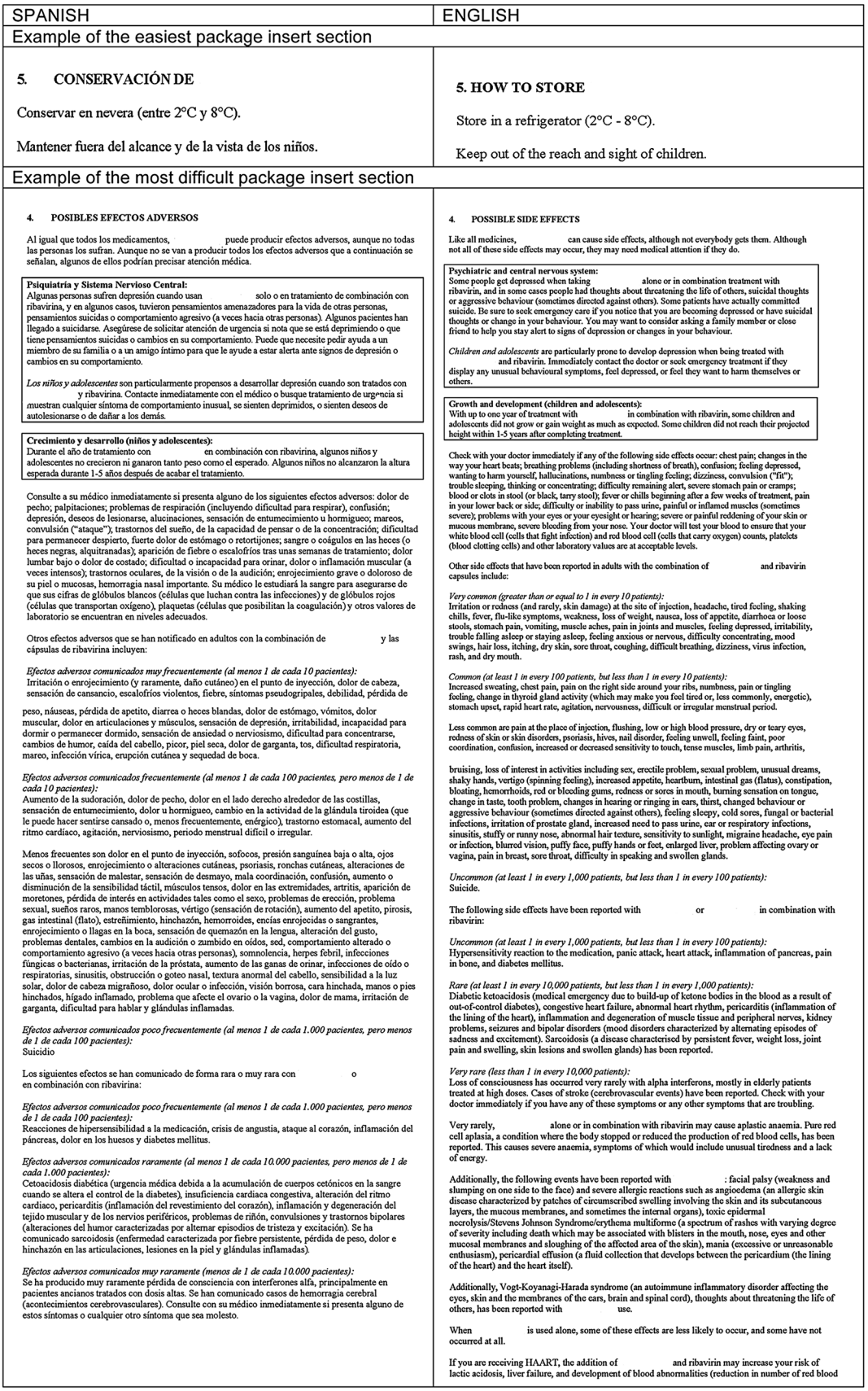
Fig. 1 Descriptive statistics of package insert sections. *SMOG* Simple Measure of Gobbledegook grade, *FKGL* Flesch-Kincaid grade level, *PERS* Szigriszt's perspicuity index

Table 4 Results obtained after Bonferroni test for multiple comparisons: *p* value

	2007					2010				
	Sec 1	Sec 2	Sec 3	Sec 4	Sec 5	Sec 1	Sec 2	Sec 3	Sec 4	Sec 5
SMOG										
Sec 2	$9.2{\cdot}10^{-1}$*	–	–	–	–	$2.0{\cdot}10^{-2}$	–	–	–	–
Sec 3	$2.0{\cdot}10^{-4}$	$1.3{\cdot}10^{-3}$	–	–	–	$4.4{\cdot}10^{-6}$	$1.6{\cdot}10^{-3}$	–	–	–
Sec 4	$5.5{\cdot}10^{-3}$	$2.6{\cdot}10^{-7}$	$2.3{\cdot}10^{-9}$	–	–	$2.5{\cdot}10^{-3}$	$1.0{\cdot}10^{-8}$	$2.0{\cdot}10^{-10}$	–	–
Sec 5	$9.6{\cdot}10^{-11}$	$2.1{\cdot}10^{-10}$	$9.4{\cdot}10^{-9}$	$3.4{\cdot}10^{-11}$	–	$3.5{\cdot}10^{-11}$	$9.7{\cdot}10^{-11}$	$3.0{\cdot}10^{-9}$	$3.1{\cdot}10^{-11}$	–
Annex	$2.0{\cdot}10^{-3}$	$3.6{\cdot}10^{-6}$	$3.5{\cdot}10^{-1}$*	$2.4{\cdot}10^{-4}$	$4.0{\cdot}10^{-2}$	$2.1{\cdot}10^{-4}$	$6.0{\cdot}10^{-4}$	$1.1{\cdot}10^{-1}$*	$7.7{\cdot}10^{-5}$	$9.0{\cdot}10^{-3}$
FKGL										
Sec 2	$7.4{\cdot}10^{-2}$*	–	–	–	–	$6.0{\cdot}10^{-4}$	–	–	–	–
Sec 3	$4.8{\cdot}10^{-6}$	$2.4{\cdot}10^{-3}$	–	–	–	$3.4{\cdot}10^{-8}$	$2.6{\cdot}10^{-4}$	–	–	–
Sec 4	$4.7{\cdot}10^{-1}$*	$2.1{\cdot}10^{-6}$	$5.3{\cdot}10^{-9}$	–	–	$5.5{\cdot}10^{-1}$*	$4.9{\cdot}10^{-6}$	$1.2{\cdot}10^{-8}$	–	–
Sec 5	$4.7{\cdot}10^{-11}$	$9.3{\cdot}10^{-11}$	$4.0{\cdot}10^{-9}$	$4.5{\cdot}10^{-11}$	–	$4.5{\cdot}10^{-11}$	$4.9{\cdot}10^{-11}$	$2.2{\cdot}10^{-10}$	$4.9{\cdot}10^{-11}$	–
Annex	$2.3{\cdot}10^{-4}$	$4.1{\cdot}10^{-4}$	$3.9{\cdot}10^{-3}$	$2.2{\cdot}10^{-4}$	$8.8{\cdot}10^{-1}$*	$8.5{\cdot}10^{-5}$	$9.7{\cdot}10^{-5}$	$7.7{\cdot}10^{-4}$	$1.1{\cdot}10^{-4}$	$1.8{\cdot}10^{-1}$*
PERS										
Sec 2	$1.2{\cdot}10^{-1}$*	–	–	–	–	$2.3{\cdot}10^{-3}$	–	–	–	–
Sec 3	$2.4{\cdot}10^{-6}$	$2.0{\cdot}10^{-3}$	–	–	–	$3.7{\cdot}10^{-8}$	$1.2{\cdot}10^{-4}$	–	–	–
Sec 4	1.000*	$3.5{\cdot}10^{-5}$	$1.1{\cdot}10^{-7}$	–	–	1.000*	$1.5{\cdot}10^{-4}$	$1.2{\cdot}10^{-9}$	–	–
Sec 5	$8.6{\cdot}10^{-11}$	$1.3{\cdot}10^{-10}$	$4.1{\cdot}10^{-9}$	$8.6{\cdot}10^{-11}$	–	$5.4{\cdot}10^{-11}$	$6.0{\cdot}10^{-11}$	$1.9{\cdot}10^{-12}$	$1.9{\cdot}10^{-14}$	–
Annex	$2.3{\cdot}10^{-4}$	$2.3{\cdot}10^{-4}$	$3.2{\cdot}10^{-4}$	$3.1{\cdot}10^{-4}$	1.000*	$8.6{\cdot}10^{-5}$	$8.6{\cdot}10^{-5}$	$3.2{\cdot}10^{-5}$	$9.3{\cdot}10^{-6}$	$1.4{\cdot}10^{-1}$*

SMOG Simple Measure Of Gobbledegook grade, *FKGL* Flesch-Kincaid grade level, *PERS* Szigriszt's perspicuity index, *Sec* package insert sections, *Sec 1* What X is and what it is used for, *Sec 2* What you need to know before you take (or use) X, *Sec 3* How to take (or use) X, *Sec 4* Possible side effects, *Sec 5* How to store X

* Not statistically significant



SPANISH	ENGLISH
Example of the easiest package insert section	
5. CONSERVACIÓN DE Conservar en nevera (entre 2°C y 8°C). Mantener fuera del alcance y de la vista de los niños.	**5. HOW TO STORE** Store in a refrigerator (2°C - 8°C). Keep out of the reach and sight of children.
Example of the most difficult package insert section	
4. POSIBLES EFECTOS ADVERSOS Al igual que todos los medicamentos, puede producir efectos adversos, aunque no todas las personas los sufran. Aunque no se van a producir todos los efectos adversos que a continuación se señalan, algunos de ellos podrían precisar atención médica. **Psiquiatría y Sistema Nervioso Central:** Algunas personas sufren depresión cuando usan solo o en tratamiento de combinación con ribavirina, y en algunos casos, tuvieron pensamientos amenazadores para la vida de otras personas, pensamientos suicidas o comportamiento agresivo (a veces hacia otras personas). Algunos pacientes han llegado a suicidarse. Asegúrese de solicitar atención de urgencia si nota que se está deprimiendo o que tiene pensamientos suicidas o cambios en su comportamiento. Puede que necesite pedir ayuda a un miembro de su familia o a un amigo íntimo para que le ayude a estar alerta ante signos de depresión o cambios en su comportamiento. *Los niños y adolescentes* son particularmente propensos a desarrollar depresión cuando son tratados con y ribavirina. Contacte inmediatamente con el médico o busque tratamiento de urgencia si muestran cualquier síntoma de comportamiento inusual, se sienten deprimidos, o sienten deseos de autolesionarse o de dañar a los demás. **Crecimiento y desarrollo (niños y adolescentes):** Durante el año de tratamiento con en combinación con ribavirina, algunos niños y adolescentes no crecieron ni ganaron tanto peso como el esperado. Algunos niños no alcanzaron la altura esperada durante 1-5 años después de acabar el tratamiento. Consulte a su médico inmediatamente si presenta alguno de los siguientes efectos adversos: dolor de pecho; palpitaciones; problemas de respiración (incluyendo dificultad para respirar), confusión; depresión, deseos de lesionarse, alucinaciones, sensación de entumecimiento u hormigueo; mareos, convulsión ("ataque"); trastornos del sueño, de la capacidad de pensar o de la concentración; dificultad para permanecer despierto, fuerte dolor de estómago o retortijones; sangre o coágulos en las heces (o heces negras, alquitranadas); aparición de fiebre o escalofríos tras unas semanas de tratamiento; dolor lumbar bajo o dolor de costado; dificultad o incapacidad para orinar, dolor o inflamación muscular (a veces intensos); trastornos oculares, de la visión o de la audición; enrojecimiento grave o doloroso de su piel o mucosas, hemorragia nasal importante. Su médico le estudiará la sangre para asegurarse de que sus cifras de glóbulos blancos (células que luchan contra las infecciones) y de glóbulos rojos (células que transportan oxígeno), plaquetas (células que posibilitan la coagulación) y otros valores de laboratorio se encuentran en niveles adecuados. Otros efectos adversos que se han notificado en adultos con la combinación de y las cápsulas de ribavirina incluyen: *Efectos adversos comunicados muy frecuentemente (al menos 1 de cada 10 pacientes):* Irritación o enrojecimiento (y raramente, daño cutáneo) en el punto de inyección, dolor de cabeza, sensación de cansancio, escalofríos violentos, fiebre, síntomas pseudogripales, debilidad, pérdida de peso, náuseas, pérdida de apetito, diarrea o heces blandas, dolor de estómago, vómitos, dolor muscular, dolor en articulaciones y músculos, sensación de depresión, irritabilidad, incapacidad para dormir o permanecer dormido, sensación de ansiedad o nerviosismo, dificultad para concentrarse, cambios de humor, caída del cabello, picor, piel seca, dolor de garganta, tos, dificultad respiratoria, mareo, infección vírica, erupción cutánea y sequedad de boca. *Efectos adversos comunicados frecuentemente (al menos 1 de cada 100 pacientes, pero menos de 1 de cada 10 pacientes):* Aumento de la sudoración, dolor de pecho, dolor en el lado derecho alrededor de las costillas, sensación de entumecimiento, dolor u hormigueo, cambio en la actividad de la glándula tiroidea (que le puede hacer sentirse cansado o, menos frecuentemente, enérgico), trastorno estomacal, aumento del ritmo cardíaco, agitación, nerviosismo, periodo menstrual difícil o irregular. Menos frecuentes son dolor en el punto de inyección, sofocos, presión sanguínea baja o alta, ojos secos o llorosos, enrojecimiento o alteraciones cutáneas, psoriasis, ronchas cutáneas, alteraciones de las uñas, sensación de malestar, sensación de desmayo, mala coordinación, confusión, aumento o disminución de la sensibilidad táctil, músculos tensos, dolor en las extremidades, artritis, aparición de moretones, pérdida de interés en actividades tales como el sexo, problemas de erección, problema sexual, sueños raros, manos temblorosas, vértigo (sensación de rotación), aumento del apetito, pirosis, gas intestinal (flato), estreñimiento, hinchazón, hemorroides, encías enrojecidas o sangrantes, enrojecimiento o llagas en la boca, sensación de quemazón en la lengua, alteración del gusto, problemas dentales, cambios en la audición o zumbido en oídos, sed, comportamiento alterado o comportamiento agresivo (a veces hacia otras personas), somnolencia, herpes febril, infecciones fúngicas o bacterianas, irritación de la próstata, aumento de las ganas de orinar, infecciones de oído o respiratorias, sinusitis, obstrucción o goteo nasal, textura anormal del cabello, sensibilidad a la luz solar, dolor de cabeza migrañoso, dolor ocular o infección, visión borrosa, cara hinchada, manos o pies hinchados, hígado inflamado, problema que afecte el ovario o la vagina, dolor de mama, irritación de garganta, dificultad para hablar y glándulas inflamadas. *Efectos adversos comunicados poco frecuentemente (al menos 1 de cada 1.000 pacientes, pero menos de 1 de cada 100 pacientes):* Suicidio Los siguientes efectos se han comunicado de forma rara o muy rara con o en combinación con ribavirina: *Efectos adversos comunicados poco frecuentemente (al menos 1 de cada 1.000 pacientes, pero menos de 1 de cada 100 pacientes):* Reacciones de hipersensibilidad a la medicación, crisis de angustia, ataque al corazón, inflamación del páncreas, dolor en los huesos y diabetes mellitus. *Efectos adversos comunicados raramente (al menos 1 de cada 10.000 pacientes, pero menos de 1 de cada 1.000 pacientes):* Cetoacidosis diabética (urgencia médica debida a la acumulación de cuerpos cetónicos en la sangre cuando se altera el control de la diabetes), insuficiencia cardiaca congestiva, alteración del ritmo cardiaco, pericarditis (inflamación del revestimiento del corazón), inflamación y degeneración del tejido muscular y de los nervios periféricos, problemas de riñón, convulsiones y trastornos bipolares (alteraciones del humor caracterizadas por alternar episodios de tristeza y excitación). Se ha comunicado sarcoidosis (enfermedad caracterizada por fiebre persistente, pérdida de peso, dolor e hinchazón en las articulaciones, lesiones en la piel y glándulas inflamadas). *Efectos adversos comunicados muy raramente (menos de 1 de cada 10.000 pacientes):* Se ha producido muy raramente pérdida de consciencia con interferones alfa, principalmente en pacientes ancianos tratados con dosis altas. Se han comunicado casos de hemorragia cerebral (acontecimientos cerebrovasculares). Consulte con su médico inmediatamente si presenta alguno de estos síntomas o cualquier otro síntoma que sea molesto.	**4. POSSIBLE SIDE EFFECTS** Like all medicines, can cause side effects, although not everybody gets them. Although not all of these side effects may occur, they may need medical attention if they do. **Psychiatric and central nervous system:** Some people get depressed when taking alone or in combination treatment with ribavirin, and in some cases people had thoughts about threatening the life of others, suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour. *Children and adolescents* are particularly prone to develop depression when being treated with and ribavirin. Immediately contact the doctor or seek emergency treatment if they display any unusual behavioural symptoms, feel depressed, or feel they want to harm themselves or others. **Growth and development (children and adolescents):** With up to one year of treatment with in combination with ribavirin, some children and adolescents did not grow or gain weight as much as expected. Some children did not reach their projected height within 1-5 years after completing treatment. Check with your doctor immediately if any of the following side effects occur: chest pain; changes in the way your heart beats; breathing problems (including shortness of breath), confusion; feeling depressed, wanting to harm yourself, hallucinations, numbness or tingling feeling; dizziness, convulsion ("fit"); trouble sleeping, thinking or concentrating; difficulty remaining alert, severe stomach pain or cramps; blood or clots in stool (or black, tarry stool); fever or chills beginning after a few weeks of treatment, pain in your lower back or side; difficulty or inability to pass urine, painful or inflamed muscles (sometimes severe); problems with your eyes or your eyesight or hearing; severe or painful reddening of your skin or mucous membrane, severe bleeding from your nose. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels. Other side effects that have been reported in adults with the combination of and ribavirin capsules include: *Very common (greater than or equal to 1 in every 10 patients):* Irritation or redness (and rarely, skin damage) at the site of injection, headache, tired feeling, shaking chills, fever, flu-like symptoms, weakness, loss of weight, nausea, loss of appetite, diarrhoea or loose stools, stomach pain, vomiting, muscle aches, pain in joints and muscles, feeling depressed, irritability, trouble falling asleep or staying asleep, feeling anxious or nervous, difficulty concentrating, mood swings, hair loss, itching, dry skin, sore throat, coughing, difficult breathing, dizziness, virus infection, rash, and dry mouth. *Common (at least 1 in every 100 patients, but less than 1 in every 10 patients):* Increased sweating, chest pain, pain on the right side around your ribs, numbness, pain or tingling feeling, change in thyroid gland activity (which may make you feel tired or, less commonly, energetic), stomach upset, rapid heart rate, agitation, nervousness, difficult or irregular menstrual period. Less common are pain at the place of injection, flushing, low or high blood pressure, dry or teary eyes, redness of skin or skin disorders, psoriasis, hives, nail disorder, feeling unwell, feeling faint, poor coordination, confusion, increased or decreased sensitivity to touch, tense muscles, limb pain, arthritis, bruising, loss of interest in activities including sex, erectile problem, sexual problem, unusual dreams, shaky hands, vertigo (spinning feeling), increased appetite, heartburn, intestinal gas (flatus), constipation, bloating, hemorrhoids, red or bleeding gums, redness or sores in mouth, burning sensation on tongue, change in taste, tooth problem, changes in hearing or ringing in ears, thirst, changed behaviour or aggressive behaviour (sometimes directed against others), feeling sleepy, cold sores, fungal or bacterial infections, irritation of prostate gland, increased need to pass urine, ear or respiratory infections, sinusitis, stuffy or runny nose, abnormal hair texture, sensitivity to sunlight, migraine headache, eye pain or infection, blurred vision, puffy face, puffy hands or feet, enlarged liver, problem affecting ovary or vagina, pain in breast, sore throat, difficulty in speaking and swollen glands. *Uncommon (at least 1 in every 1,000 patients, but less than 1 in every 100 patients):* Suicide. The following side effects have been reported with or in combination with ribavirin: *Uncommon (at least 1 in every 1,000 patients, but less than 1 in every 100 patients):* Hypersensitivity reaction to the medication, panic attack, heart attack, inflammation of pancreas, pain in bone, and diabetes mellitus. *Rare (at least 1 in every 10,000 patients, but less than 1 in every 1,000 patients):* Diabetic ketoacidosis (medical emergency due to build-up of ketone bodies in the blood as a result of out-of-control diabetes), congestive heart failure, abnormal heart rhythm, pericarditis (inflammation of the lining of the heart), inflammation and degeneration of muscle tissue and peripheral nerves, kidney problems, seizures and bipolar disorders (mood disorders characterized by alternating episodes of sadness and excitement). Sarcoidosis (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported. *Very rare (less than 1 in every 10,000 patients):* Loss of consciousness has occurred very rarely with alpha interferons, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms or any other symptoms that are troubling. Very rarely, alone or in combination with ribavirin may cause aplastic anaemia. Pure red cell aplasia, a condition where the body stopped or reduced the production of red blood cells, has been reported. This causes severe anaemia, symptoms of which would include unusual tiredness and a lack of energy. Additionally, the following events have been reported with : facial palsy (weakness and slumping on one side to the face) and severe allergic reactions such as angioedema (an allergic skin disease characterized by patches of circumscribed swelling involving the skin and its subcutaneous layers, the mucous membranes, and sometimes the internal organs), toxic epidermal necrolysis/Stevens Johnson Syndrome/erythema multiforme (a spectrum of rashes with varying degree of severity including death which may be associated with blisters in the mouth, nose, eyes and other mucosal membranes and sloughing of the affected area of the skin), mania (excessive or unreasonable enthusiasm), pericardial effusion (a fluid collection that develops between the pericardium (the lining of the heart) and the heart itself). Additionally, Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord), thoughts about threatening the life of others, has been reported with use. When is used alone, some of these effects are less likely to occur, and some have not occurred at all. If you are receiving HAART, the addition of and ribavirin may increase your risk of lactic acidosis, liver failure, and development of blood abnormalities (reduction in number of red blood

Fig. 2 Samples of the easiest and most difficult to read package insert sections

, solo o en combinación con ribavirina, muy raramente puede causar anemia aplásica. Se ha comunicado aplasia de la serie roja, que es una enfermedad en la que el cuerpo interrumpe o disminuye la producción de glóbulos rojos. Esto produce anemia grave, cuyos síntomas incluirían cansancio inusual y falta de energía.

Además se han comunicado las siguientes reacciones con : parálisis facial (debilidad y depresión de un lado de la cara) y reacciones alérgicas graves tales como angioedema (una enfermedad de la piel de tipo alérgico caracterizada por zonas de hinchazón delimitada que afectan a la piel y sus capas subcutáneas, las membranas mucosas, y a veces a los órganos internos), necrólisis epidérmica tóxica/Síndrome de Stevens Johnson/eritema multiforme (una gama de erupciones cutáneas de distinto grado de gravedad incluyendo la muerte, que pueden ir asociadas con ampollas en la boca, nariz, ojos y otras mucosas, y escarificación de la zona afectada de la piel), manía (entusiasmo excesivo o poco razonable), derrame pericárdico (acumulación de líquido que se localiza entre el pericardio (el revestimiento del corazón) y el propio corazón).

Además, se ha comunicado con el uso de el síndrome de Vogt-Koyanagi-Harada (una enfermedad inflamatoria autoinmune que afecta a los ojos, piel y membranas de los oídos, cerebro y médula espinal), pensamientos amenazadores para la vida de otras personas.

Cuando se utiliza solo, es menos probable que se produzcan algunos de estos efectos, y algunos no han ocurrido nunca.

Si está recibiendo TARGA (terapia antirretroviral de gran actividad), la adición de y ribavirina puede aumentar el riesgo de acidosis láctica, fallo hepático y desarrollo de alteraciones sanguíneas (reducción del número de glóbulos rojos que transportan oxígeno, de ciertos glóbulos blancos que combaten las infecciones y de células sanguíneas para la coagulación llamadas plaquetas).

Los siguientes efectos adversos (no mencionados anteriormente) se han producido con la combinación de y ribavirina cápsulas (adultos) en pacientes coinfectados con VHC/VIH que recibían TARGA (terapia antirretroviral de gran actividad):
candidiasis oral (aftas bucales), metabolismo deficiente de las grasas, disminución de los linfocitos CD4, pérdida de apetito, dolor de espalda, hepatitis, dolor en las extremidades y diversos valores sanguíneos anormales en pruebas de laboratorio.

Las siguientes reacciones se han producido con la combinación de /ribavirina en niños y adolescentes:

Efectos adversos comunicados muy frecuentemente (al menos 1 de cada 10 pacientes):
Pérdida de apetito, vértigos, dolor de cabeza, vómitos, náuseas, dolor de estómago, caída del cabello, piel seca, dolor en articulaciones y músculos, enrojecimiento en el punto de inyección, irritabilidad, sensación de cansancio, malestar, dolor, escalofríos, fiebre, síntomas pseudogripales, debilidad, pérdida de peso, reducción del número de glóbulos rojos que pueden causar fatiga, dificultad respiratoria.

Efectos adversos comunicados frecuentemente (al menos 1 de cada 100 pacientes, pero menos de 1 de cada 10 pacientes):
Infección por hongos, resfriado común, herpes febril, faringitis (dolor de garganta), sinusitis, infecciones de oído, reducción de células sanguíneas para la coagulación llamadas plaquetas que pueden provocar fácilmente moratones y sangrado espontáneo, inflamación de las glándulas (nódulos linfáticos inflamados), comportamiento agresivo, agitación, ira, alteración del humor, nerviosismo o inquietud, depresión, ansiedad, dificultad para dormir o permanecer dormido, inestabilidad emocional, sueño deficiente, sensación de sueño, alteración de la atención, alteración del gusto, sensación de desmayo, dolor de ojos, palpitaciones (latidos violentos), latido rápido del corazón, sofocos, tos, sangrado de nariz, dolor de garganta, llagas en la boca, labios agrietados y grietas en las comisuras de la boca, diarrea, malestar de estómago, dolor de boca, erupción, enrojecimiento de la piel, picor, eczema (piel inflamada, roja, con picor y seca, con posibles lesiones que supuran), acné, dolor de espalda, dolor muscular y de huesos, dolor en las extremidades, sensación de frío, sequedad, dolor, erupción,

irritación o picor en la zona de la inyección, alteraciones en las pruebas de tiroides, disminución de la actividad de la glándula tiroidea que le puede hacer sentirse cansado, deprimido, aumentar su sensibilidad al frío así como otros síntomas.

Efectos adversos comunicados poco frecuentemente (al menos 1 de cada 1.000 pacientes, pero menos de 1 de cada 100 pacientes):
Picores en la zona anal (lombrices o ascarides), enrojecimiento, inflamación, dolor en la piel, herpes, dificultad para respirar, dolor o dificultad al orinar, ganas frecuentes de orinar, inflamación de la membrana que reviste el estómago y los intestinos, comportamientos anormales, desórdenes emocionales, miedos, pesadillas, temblores, disminución de la sensibilidad al tacto, sensación de entumecimiento u hormigueo, dolor que irradia a lo largo del curso de uno o más nervios, somnolencia, sangrado de las membranas de la mucosa que une la superficie interior de los párpados, picor de ojos, dolor de ojos, visión borrosa, intolerancia a la luz, presión sanguínea baja, palidez, malestar nasal, goteo nasal , respiración sibilante, encías inflamadas, inflamación del hígado, piel sensible a la luz solar, erupción cutánea con lesiones con manchas abultadas, decoloración de la piel, descamación de la piel, reducción del tejido muscular, contracciones musculares, presencia de un exceso de proteínas en la orina, menstruación dolorosa, dolor o malestar en el pecho, dolor facial, moratones.

Si considera que alguno de los efectos adversos que sufre es grave o si aprecia cualquier efecto adverso no mencionado en este prospecto, informe a su médico o farmacéutico.

cells which carry oxygen, certain white blood cells that fight infection, and blood clotting cells called platelets).

The following other side effects (not listed above) have occurred with the combination of and ribavirin capsules (adults) in HCV/HIV co-infected patients receiving HAART: oral candidiasis (oral thrush), defective metabolism of fat, CD4 lymphocytes decreased, appetite decreased, back pain, hepatitis, limb pain, and various laboratory blood values abnormalities.

The following effects have occurred with the combination of /ribavirin in children and adolescents:

Very common (greater than or equal to 1 in every 10 patients):
Loss of appetite, dizziness, headache, vomiting, nausea, stomach pain, hair loss, dry skin, pain in joints and muscles, redness at the site of injection, feeling irritable, tired feeling, feeling unwell, pain, chills, fever, flu-like symptoms, weakness, decreased weight, decreases in red blood cells that may cause fatigue, shortness of breath, dizziness.

Common (at least 1 in every 100 patients, but less than 1 in every 10 patients):
Fungal infection, common cold, cold sores, pharyngitis (sore throat), sinusitis, ear infection, decrease in blood clotting cells called platelets, that may result in easy bruising and spontaneous bleeding, swollen glands (swollen lymph nodes), aggressive behaviour, agitation, anger, mood changes, nervousness or restlessness, depression, feeling anxious, trouble falling asleep or staying asleep, emotional instability, poor quality sleep, feeling sleepy, disturbance in attention, changes in taste, fainting, eye pain, palpitations (pounding heart beat), rapid heart rate, flushing, coughing, nosebleed, throat pain, sores in mouth, scaling lips and clefts in the corners of the mouth, diarrhoea, stomach upset, oral pain, rash, redness of skin, itching, eczema (inflamed, red, itchy and dryness of the skin with possible oozing lesions), acne, back pain, muscle and bone pain, limb pain, feeling cold, dryness, pain, rash, irritation or itching at the site of injection, blood thyroid tests abnormalities, decrease in thyroid gland activity, which may make you feel tired, depressed, increase your sensitivity to cold and other symptoms.

Uncommon (at least 1 in every 1000 patients, but less than 1 in every 100 patients):
Itchy anal area (pinworms or ascarids), redness, swelling, pain of skin, shingles, difficult breathing, painful or difficult urination, urinary frequency, inflammation of the lining membrane of the stomach and the intestines, abnormal behaviour, emotional disorder, fear, nightmare, tremor, decreased sensitivity to touch, numbness or tingling feeling, pain radiating along the course of one or more nerves, drowsiness, bleeding of the mucous membrane that lines the inner surface of the eyelids, itchy eyes, eye pain, blurred vision, intolerance to light, low blood pressure, paleness, nasal discomfort, runny nose, wheezing, inflamed gums, enlarged liver, skin sensitive to sunlight, rash with raised spotted lesions, skin discolouration, peeling of skin, shortening of muscle tissue, muscle twitching, the presence of excess protein in the urine, painful menstruation, chest pain or discomfort, facial pain, bruising.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Fig. 2 continued

PERS was used to analyse the results qualitatively. It showed that section 4 was rather difficult to understand, section 1 was standard in 2007 and rather difficult in 2010, sections 2 and 3 corresponded to the category of standard, the annex was rather easy to understand, and section 5 was rather easy in 2007 and easy in 2010. Figure 2 shows samples of the easiest and the most difficult to read package insert sections for basiliximab and peginterferon alfa-2b in both Spanish and English.

Thus, sections 1 and 4 of the package inserts were found to be the most difficult sections to understand. These sections contain information related to the therapeutic indications and potential adverse drug reactions, respectively, which patients consider important [24]. In addition, we demonstrated that the readability decreased substantially in sections (1 and 4) over this period (SMOG and FKGL increased, and PERS decreased; Table 3). In contrast, the easiest section to understand (Storage) contains information that patients consider less important [24]. Finally, since all the mean values of PERS for each medicine were under 75 (Table 2), no package insert was easy to understand.

It was also observed that, in the majority of cases, the reading grade levels obtained using SMOG were slightly higher than those obtained using FKGL. This corresponds to the fact that McLaughlin [20] established SMOG to calculate the reading grade levels required of a reader to ensure complete comprehension (100 % expected comprehension); whereas Kincaid et al. [21] established FKGL in such a way that the reading grade level obtained resulted in more than one readability level lower than other formulas (35 % expected comprehension). This is an important aspect, given that FKGL may overestimate the readability and, in this way, be a less adequate formula for the assessment of written materials related to healthcare, in

which 100 % comprehension on the part of the target population is hoped for [19]. This situation is repeated in different studies related to health literacy where differences of up to three reading grade levels have been reported in texts written in English, depending on the readability formula used [9, 13, 25].

Our results show FKGL and PERS to be the most closely correlated indices, probably because the ways in which they estimate their indices are very similar (both formulas use the same variables to calculate an index).

4.1 Limitations

One of the limitations of the present study is that comprehension of the texts was not tested in a sample of patients from the target population; of particular importance considering that user testing is required in the EU. Tools are also available that allow an assessment of the information contained on package inserts by patients, such as the Consumer Information Rating Form (CIRF) [26] and the Package Insert Test (PAINT) [27]. Nevertheless, Smith et al. [28] confirmed their results regarding the evaluation of patient information materials from readability formulas through user testing, thereby lending weight to the former as a valid indication of the latter.

However, independent of direct patient understanding, we could have taken into account the availability of features designed to facilitate a better understanding of the texts, such as illustrations, tables, diagrams, graphs, and the original type of format, compared with a package insert with no format, which is how we applied the readability formulas. Instruments are available to assess the use of all such information (e.g. the Suitability Assessment of Materials [29]) used in numerous studies to analyse the suitability of print resources related to health [30–32]. Nevertheless, in that tool, the scoring process is subjective for most evaluative criteria, and it does not consider the quality and scientific accuracy of the written information [31]. More recently, another indirect instrument called The Patient Education Materials Assessment Tool (PEMAT) has been designed to be completed by professionals as a means of assessing the understandability and actionability of educational print and audiovisual materials aimed at patients. The tool provides a guide to help determine whether patients will be able to understand and act on the information provided [33]. However, three readability formulas were selected, the way in which they were applied is explained and, in order to prevent problems of interpretation that may arise due to an unsuitable selection of a sample or of information that may be more or less relevant depending on the patient, all the information contained in the selected package inserts was used to obtain the readability scores used.

Furthermore, although the tools listed above to establish the readability of package inserts (completed by patients or professionals) are very useful, readability formulas allow us to predict the level of difficulty of written materials in a simple way [34], and could be used as a complementary tool in the analysis of healthcare information.

Finally, a limitation to be borne in mind is that our study examines a sample of biological medicinal products that were commercially available in 2007. Nevertheless, it is important to consider that the 33 medicines derived from biotechnology processes selected continue to be authorised.

5 Conclusion

The readability scores of the package inserts for the biological medicinal products available on the EMA website assessed here remain above the sixth grade reading level (SMOG and FKGL higher; PERS lower). This highlights the poor quality of the package inserts, which may lead to difficulties of understanding for people with limited literacy skills.

In spite of the requirement that package inserts be easy to read, and the recommendations on various aspects related to the preparation of package inserts set out in the 2009 EC guideline, including the syntax, no improvement was observed 1 year after that guidance came into effect. None of the package inserts assessed was easy to understand, and differences between the package insert sections were observed. Some of them, which contained information considered important by the patient, being rather difficult to understand.

All the sections should be easy to read; therefore the readability of package inserts for the medicines studied need to be improved so that they can be understood by those who receive them, thereby contributing to safe and appropriate use of medicines and improved patient health outcomes. Major efforts are required by pharmaceutical companies, authorities and regulatory bodies in order to ensure the leaflets for biological medicinal products are comprehensible to patients.

Author contributions M[a]. Angeles Piñero-López acquired, analyzed and interpreted data; and drafted and approved the final submitted manuscript. Pilar Modamio conceived of the study, analyzed and interpreted data, and drafted and approved the final submitted manuscript. Cecilia F. Lastra made suggestions for data interpretation and approved the final submitted manuscript. Eduardo L. Mariño conceived of the study, analyzed and interpreted data, and drafted and approved the final submitted manuscript.

Conflicts of interest M[a]. Ángeles Piñero-López, Pilar Modamio, Cecilia F. Lastra and Eduardo L. Mariño have no conflicts of interest that are directly relevant to the content of this study. The authors certify that no funding has been received for the conduct of this study

and/or preparation of this manuscript. The authors have full control of all primary data and they agree to allow the journal to review their data if requested.

The manuscript does not contain clinical studies or patient data.

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