

Example: Production location: Söğütözü/Çankaya/Ankara

**GUIDELINE ON PACKAGING INFORMATION AND INSTRUCTIONS FOR USE OF MEDICINAL
PRODUCTS FOR HUMAN USE GUIDELINE ON THE READABILITY OF THE PACKAGING
INFORMATION AND INSTRUCTIONS FOR USE OF MEDICINAL PRODUCTS FOR HUMAN USE
GUIDELINE ON EXCIPIENTS ON THE PACKAGING INFORMATION AND INSTRUCTIONS FOR USE OF
MEDICINAL PRODUCTS FOR HUMAN USE**

İRD-KLVZ-07

Document No. First Issue Date Revision Date Revision No Page İRD-KLVZ-07

First Version Effective Date 14.07.2017 First Revision Effective Date 11.09.2017 Second
Revision Effective Date 02.10.2017 Third Revision Effective Date 23.02.2018 Fourth Revision
Effective Date 18.12.2018 Fifth Revision Effective Date 23.01.2019 Sixth Revision Effective Date
18.04.2020 Seventh Revision Effective Date 15.11.2022 Eighth Revision Effective Date 23.05.2023
Ninth Revision Effective Date 28.07.2023 Tenth Revision Effective Date 03.10.2023 Eleventh
Revision Effective Date 26.02.2024 Twelfth Revision Effective Date 10.06.2024 Thirteenth Revision
Effective Date 18.09.2024 Fourteenth Revision Effective Date 06.12.2024 Fifteenth Revision
Effective Date 10.11.2025

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14/07/2017

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INTRODUCTION

This guideline has been prepared on the basis of Article 20 of the Regulation on Packaging Information, Instructions for Use and Follow-up of Medicinal Products for Human Use published in the Official Gazette dated 25.04.2017 and numbered 30048, to be implemented together with the aforementioned Regulation, to assist applicants/license/permit

holders in creating packaging information, instructions for use and packaging sample

The guide consists of three parts. The first section explains how the provisions of the Regulation on Packaging Information, Instructions for Use and Follow-up of Medicinal Products for Human Use are implemented.

The second part provides guidance on ensuring that the information on the packaging and instructions for use is clear so that medicinal products for human use can be used safely and appropriately.

Third part contains explanations on the presence of certain excipients in medicinal products for human use.

SECTION 1

GUIDELINE ON PACKAGING INFORMATION and INSTRUCTIONS FOR USE OF MEDICINAL PRODUCTS FOR HUMAN USE

Purpose

The purpose of this section is to clarify the relevant provisions of the Regulation. Issues Regarding Packaging Information and Instructions for Use Specified in the Regulation

1. Name of Medicinal Product for Human Use

- The name of each medicinal product for human use for which license has been applied for or granted should be chosen in such a way as to avoid any confusion with the name of any other medicinal product for human use.

- The license/permit name of the medicinal product for human use accepted by the Agency must include the following:

The name of the medicinal product for human use, its strength, pharmaceutical form and, where applicable, information on whether it is intended for infants, children or adults.

- The name of the medicinal product for human use may be one of the following:

- o A trade name invented to avoid confusion with the common name of the medicinal product for human use,

- o The name of the marketing authorization/permit holder/licensor of the medicinal product for human use or the common name given with the trademark,

A packaging sample is a full-color, two-dimensional drawing that can be cut and folded to create an exact copy of the packaging that will be put on the market, after cutting and folding when necessary, providing a copy of the immediate and outer packaging to ensure that the three-dimensional presentation of the packaging information text prepared with the information subject to the license/permit is clear.

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- o The name of the marketing authorization/permit holder/licensor of the medicinal product for human use or the scientific name given with the trademark,

- In cases where there is only one strength or pharmaceutical form, the strength and pharmaceutical form should be added to the name of the medicinal product for human use. • It is recommended that this information be given in the following order without compromising the integrity of the name:

"The name of the medicinal product for human use, its strength, information that it is intended for infants, children or adults, where applicable, and its pharmaceutical form" and the common name of the active substance, as appropriate

Example 1: XXX 10 mg/mL Pediatric Syrup

Example 2: Ichthyol XXX 10% Pomade

- In cases where the medicinal product for human use contains up to three active substances, the common name(s) of the active substance(s) must be indicated in the packaging information following the full name, unless the common name(s) of the active substance(s) is part of the name of the medicinal product for human use. The common name(s) of the active

substance(s) may be written below the full expression of the name/strength/pharmaceutical form. For security reasons, special attention should be paid to the International Nonproprietary Name (INN). • If the medicinal product for human use contains more than three active substances (e.g., multivitamins), these active substance names may be positioned in a different place on the outer packaging. • If the appearance of the name is integrated into the same field of view, this information can be presented on different lines of text or in different font sizes.

Example:

Name A mg/mL

Solution for Injection

Name A mg/mL

Solution for Injection Name A mg/mL Solution for Injection Name A mg/mL

Solution for Injection Name A mg/mL Name A mg/mL

Common name of active substance

Solution for Injection NAME INTEGRITY BROKEN Sol Inj

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• The List of Standard Terms of the European Pharmacopoeia should be used for pharmaceutical forms. The list of Standard Terms includes short terms for some pharmaceutical forms, but these short terms should only be used where there is insufficient space to print the full standard term in 7-point font size on the package (e.g. on blisters and small packages)

2. Active Substance

The active substance should be indicated using its common name. The common name is the INN recommended by the World Health Organization or, where the INN is not available, the name of the active substance in classical sources that are scientifically accepted as references.

3. Quantitative Expression of Active Substance • The amount of active substance should be expressed in one of the following:

- Per dosage unit
- Per specific volume according to the type of application
- Per specific weight according to the type of application

• The active substance of the medicinal product for human use must be indicated in the formula. It does not need to be indicated elsewhere on the packaging. Example: "500 mg paracetamol"

• For an active substance presented in the form of a compound or derivative (e.g., salt or ester), the amount of the salt or ester should be expressed in equivalents. Example: "63.5 mg toremifene citrate equivalent to 60 mg toremifene"

• Different strengths of the same medicinal product for human use should be expressed in the same unit of measurement. Example 1: 250 mg, 500 mg, 750 mg and 1000 mg Example 2: 1 g and 2 g

• Zeros after commas should not be specified. Example: 2.5 mg NOT 2.50 mg

• The use of decimal points (or commas) should be avoided as they are easily erasable. Example: 250 mg instead of 0.25 g or 0.25 g

• For safety reasons, micrograms should always be written in full (micrograms) or abbreviated as "mcg" instead of the abbreviation (µg). • However, in certain situations that cannot be resolved using smaller font size (≤7), the abbreviated form "µg" may be used, provided that it is justified and there are no safety concerns. • I.U. or U. should be used where applicable. However, all products containing Polymyxin group antibiotics must indicate the amount of active substance in the form of I.U. or U.

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3.1. Parenteral Medicinal Products for Human Use

- For single-dose parenteral products, the amount of active substance(s) must be indicated per total volume.
- For multiple dose and large volume parenteral products, the amount of active substance(s) should be indicated per mL and, as appropriate, per mL, 100 mL, 1000 mL, etc.
- For large volume parenteral products containing inorganic salts, the amount of these salts should also be indicated in millimoles.

3.2. Concentrates for Parenteral Use

- For parenteral products containing concentrated active substance(s) (e.g., concentrated hemodialysis solution), packaging information should indicate the content of the active substance(s) per mL and the total content. For parenteral products that must be used after dilution, there must be a clear statement that takes dilution into account. For example, "It must be diluted before use. See instructions for use".
- The following information should be indicated on the packaging information:

- Total content of the active substance(s) in the concentrate,
- Total content of active substance(s) per mL of concentrate.

3.3. Powder for Reconstitution Prior to Parenteral Use

- The packaging information of parenteral products containing the active substance(s) in powder form to be reconstituted should include the following:

- The total content of the active substance(s) in the container,
- "When reconstituted as recommended, X mg of active substance per mL is obtained", (unless various reconstitution routes are available resulting in different final concentrations).

- There must be a clear statement that the instructions for use should be consulted for information on reconstitution.

3.4. Transdermal Patches

Each of the following numbers must be presented separately and clearly. This way they can be easily distinguished from each other, otherwise they may cause confusion during the preparation phase.

- Content of the active substance(s) contained in each patch,
- Average dose given to the patient per unit time (hour, day, etc.) (i.e., absorbed dose)
- Adhesion surface

3.5. Multidose Solid or Semi-Solid Medicinal Products for Human Use

Example: Powder, granules, cream and ointment.

The amount of the active substance(s) should be indicated per unit dose where possible, or per gram or percentage where not possible.

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3.6. Implants and Intrauterine Devices Classified as Medicinal Products for Human Use

The amount of active substance(s) should be expressed as follows:

- The content of the active substance(s) contained in each product,
- Average dose given to the patient per unit time (hour, day, etc.) (i.e., released and absorbed dose)
- Total time (hours, days, etc.) that this average dose is expected to be given.

4. Pharmaceutical Form and Content by Weight, Volume or Number of Doses

- The List of Standard Terms of the European Pharmacopoeia should be used. The List of Standard Terms includes short terms for some pharmaceutical forms, but these short terms should only be used when there is insufficient space to print the full standard term in 7-point type on the package (for example, on blisters and small packages).
- The contents should be expressed in terms of weight, volume, number of doses (number of doses for solutions, number of doses or sprays for inhalers, etc.), number of administration units, package size.
- The unit quantity

contained in the package, such as the number of tablets, ampoules, vials, etc., shall be indicated numerically; for pharmaceutical forms whose net content cannot be counted, the content shall be indicated as volume or weight or number of doses. For aerosols, the net amount is given by weight; for metered aerosols, the number of doses and each metered dose is written. For medicinal products for human use taken orally by drop, the number of drops per milliliter is given. For semi- solid pharmaceutical forms such as ointments and creams, the net content is given in grams.

5. Excipients to be Specified

See Section 3 - Guidance on Excipients in the Package Information and Instructions for Use of Medicinal Products for Human Use.

6. Implementation Method and, if necessary, Implementation Pathway

- Method of administration is the general method by which the medicinal product for human use is intended to be administered to the patient. For example: inhalation, injection
- Route of administration is the route by which the medicinal product for human use is taken into or comes into contact with the body. For example, intravenous, oral, ocular
- Some information on the method of administration is particularly necessary for non- prescription medicinal products for human use.
- The route of administration must be indicated in the short product information only as recorded according to standard terms. Negative statements alone and/or in isolation should not be used: For example, "not for intravenous use". Basically, only standard abbreviations are acceptable (i.v., i.m., s.c.). the spelling "IM" or "I.M." or "i.m." or "im" is acceptable.
- Other non-standard ways of implementation should be written in full. Some routes of administration are not familiar to patients and should be described in the instructions for use. This is particularly important for non- prescription medicinal products for human use.
- The European Pharmacopoeia Standard Terminology List should be used for the method and route of administration.

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7. Storage Conditions

- Storage warnings must be in accordance with the summary of product characteristics (SmPC).
- The following are some of the storage condition statements that should be used:

- Store at room temperature below 25°C.
- Store at room temperature below 30°C.
- Store in the refrigerator between 2°C-8°C.
- Store in the freezer.
- Do not freeze.
- Keep in the original packaging.

- Where appropriate, storage conditions statements should include an additional brief explanation in a user-friendly manner (e.g., to protect from light/moisture). For medicinal products for human use where a warning is required, there should be a warning about the symptoms of product degradation. For example, a product whose pharmaceutical form is a solution may require a warning such as "Do not use if precipitate is observed."

8. License/Permit Holder

- The license holder may give his/her address as "neighborhood/district/province" or "district/province".
- In addition to the name and address of the license holder, the phone number and/or registered electronic mail (KEP) address of the license/permit holder may also be written on the packaging information and the instructions for use, provided that this does not affect the readability of the mandatory text.

9. Name and Address of Production (Manufacturing) Place

- As the address of the place of production (manufacturing), it is sufficient to write neighborhood/district/province or district/province for products produced in our country, neighborhood/district/province/country or district/province/country for imported products. • It is not mandatory to write the name of the solvent production site on the outer packaging. • it can be expressed as "place of production" or "place of manufacture".

or

10. License/Permit Number Information

- It contains the date and number of the license/permit respectively. It can be expressed as "License no" or "License number" or "Permit no" or "Permit number". Either "." or "/" can be used between the day, month and year in date writing.

Example: License number: 01/01/2015- 2015/1

or

License no: 01/01/2015- 2015/1

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- For products licensed for manufacturing within the scope of localization, the license number information may not be included on the inner packaging for enough series to ensure the security of supply of the medicine.

11. Batch Number

a. It can be expressed as "Batch number" or "Batch no". b. For detailed information, see "Barcode and QR Code Application Guide for Medicinal Products for Human Use"

12. Expiry Date

12.1. Expiration Date Expression

12.1.1. The expiry date may not be written elsewhere on the outer packaging for a second time if it is included in visually readable codes next to the QR code.

12.1.2. If the expiration date is to be written separately, it shall be indicated in accordance with the date on the QR code. 12.1.3. If the expiry date is to be indicated as MM/YYYY on the outer packaging, it must be written in the QR code as the last day of the month preceding the date set as the expiry date. If it is to be specified in readable codes, it should be expressed as MM.YYYYY. If it is not included in the visually readable codes, it should be stated on the outer packaging, and if it is desired to be stated separately on the outer packaging, it should be stated in the relevant field as MM/YYYY, MM.YYYYY or month in writing and year in numbers (4 digits).

Example: For a medicinal product for human use with an expiry date of May 29, 2017, the expiry date in the QR code should be April 30, 2017. If it is to be specified in readable codes, it should be expressed as 04.2017. If it is not included in the visually readable codes or if it is desired to be indicated separately on the outer packaging, it should be expressed as 04/2017 or April 2017.

12.1.3.1. The expiry date printed on products with the month and year shall be considered as the last day of that month.

12.1.3.2. If the expiry date falls on the last day of the month, the previous month does not need to be written.

12.1.4. If the expiry date is to be indicated on the outer packaging as DD/MM/YYYY, the expiry date must be written exactly in the QR code. If it is to be specified in readable codes, it should be expressed as DD.MM.YYYYY. If it is not included in the visually readable codes or if it is desired to be indicated separately on the outer packaging, it should be expressed as DD/MM/YYYY.

Example: For a medicinal product for human use with an expiry date of May 14, 2017, the expiry date in the QR code should be May 14, 2017. If it is to be specified in readable codes, it should be expressed as 14.05.2017. If it is not included in the visually readable codes or if it is

desired to be indicated separately on the outer packaging, it should be expressed as 14/05/2017 or 14 May 2017.

12.1.5. The expiry date can be expressed on the outer packaging as 2 digits or at least 3 characters of month and 4 digits of year.

Example: Feb -2001, Feb-2001, 02- 2001

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12.1.6. The expiry date on the inner packaging is in line with the date on the QR code. For products consisting of a powder and a solvent, the expiry date of the solvent must be the same or later than the expiry date of the powder. For products whose justification is deemed appropriate by the Agency, the expiry date of the powder or solvent may be written on the outer packaging of products consisting of a powder and a solvent.

12.2. Shelf Life During Use

c. The maximum shelf life of products whose stability decreases following dilution, reconstitution or opening of the can should be indicated. The packaging information should state "Once opened/diluted/reconstituted, it should be used within ... days/hours provided that it is stored below ... °C.". In certain cases that cannot be resolved using smaller font size (≤ 7), a statement such as "read the instructions for use for the shelf life of the reconstituted product" should be included in the packaging information, provided that it is justified and there are no safety concerns. ç. For certain products, such as radiopharmaceuticals and some vaccines, it may be necessary to detail the shelf-life following dilution, reconstitution or opening of the package (e.g. minutes, hours, days, months and years)

13. "Sterile" for sterile products and "apyrogenic" for apyrogenic products shall be written on the outer and inner packaging and instructions for use. For cytotoxic products, "cytotoxic" record is placed on the outer and inner packaging and instructions for use.

The outer packaging of high- risk medicinal products for human use may be marked to indicate that these products are high-risk.

14. Unused medicinal products for human use or wastes of medicinal products for human use must be disposed of in accordance with the provisions of the Waste Management Regulation published in the Official Gazette dated 2/4/2015 and numbered 29314. On the instructions for use, it is stated "Do not throw expired or unused medicines in the garbage! Give them to the collection system designated by the Ministry of Environment and Urbanization". On the instructions for use, it is stated "Wastes from the empty inner packaging of cytotoxic and cytostatic medicinal products for human use are DANGEROUS WASTES and these wastes are managed according to the Waste Management Regulation published in the Official Gazette dated 2/4/2015 and numbered 29314."

15. In all cases that require an update to the Instructions for Use, the Instructions for Use shall be submitted to the Agency for approval. Instructions for use approved by the Agency shall be published by changing the update date.

16. In addition to the instructions for use of medicinal products for human use, patient warning card 2 and user manual can be found where necessary, if specified by the Agency.

2 Patient Warning Card: This refers to a card attached to the outer packaging or independent of the outer packaging containing important information about the medicinal product for human use, which the patient must carry with him/her at all times in order to inform any physician or dentist treating him/her about the treatment he/she is receiving.

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17. Symbols and Other Information under Article 9 of the Regulation on Packaging Information, Instructions for Use and Follow-up of Medicinal Products for Human Use

a. Symbols or pictorial diagrams that are useful for patients and are intended to clarify packaging information and other information consistent with the brief product information, other than elements that may be incentive and/or promotional, may be included in the package information and instructions for use, provided that they are submitted to and approved by the

Agency.

b. Products whose instructions for use indicate that they may impair or impede the ability to drive or operate machinery require a symbol (warning triangle) on the outer packaging (Figure 1, Figure 2 and Figure 3). The size of the warning triangle should be determined taking into account the box design and readability. The warning triangles are classified into 3 categories in terms of the level of risk of driving according to their active substances.

c. Active substances and "Vehicle Warning Triangles ATC Code Level List," prepared according to ATC codes, is published on the Agency's official website.

o First level "yellow" warning triangle

The risk for driving is low and largely depends on the sensitivity of the person. The drug usually does not affect driving. However, patients should be informed of this risk before driving (First level active substances).

o Second level "orange" warning triangle

Pharmacodynamic effects dangerous for driving vary according to the sensitivity of the individual. The suitability of the drug for vehicle use should be assessed on a case-by-case basis. In some cases, the medicine may affect the ability to drive and a healthcare professional should be consulted (Second level active substances).

o Level three "red" warning triangle

Do not drive without reading the instructions for use Do not drive without consulting a healthcare professional Ask your doctor when you can drive again Attention: Do not drive Be very careful Be careful LEVEL 1 LEVEL 2 LEVEL 3

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The pharmacodynamic effects of the drug make driving dangerous. It is strongly recommended not to drive during treatment. The healthcare professional is advised to inform the patient when they can drive again, taking into account any possible residual effects. (e.g. how long after a sleep induced by a hypnotic drug) (Third level active substances)

The following pictogram, which does not contain risk level information, should be added to the outer packaging of medicinal products for human use containing active substances that have an effect on the use of vehicles and machinery, although not listed as level one, two or three.

18. Within the scope of the Regulation, "Main treatment group" is not included among the information required on the inner and outer packaging. Therefore, it is not appropriate to write the main treatment group of the medicinal product for human use on the inner and outer packaging.

19. In cases where animal sources are used in the active and auxiliary substances of medicinal products for human use, this source must be specified in the Instructions for Use: In the Instructions for Use, the active and auxiliary substances contained in each dosage unit of the medicinal product for human use or in a certain volume or weight according to the form of application are expressed qualitatively, while the name of the animal source used in the active and auxiliary substance must be clearly stated. For the active substance, this information is also given in the "What is ... and what is it used for?" section of the Instructions for Use.

Example 1: Bovine bile extract; pancreatin (pancreatic powder produced from bovine pancreatic tissue); gelatin (fish gelatin).

Example 2: Equine rabies antiserum (rabies immunoglobulin purified from post - injection plasma of horses injected with rabies vaccine)

20. In order to accurately determine the amount of water to be added to the product, a notch should be added to the inner packaging of products whose pharmaceutical form is dry powder for the preparation of suspension and products prepared by reconstitution; or this point should be indicated by appropriate marking (such as a line) on the inner packaging label.

21. It will ensure that the packaging integrity of the outer packaging of medicinal products for human use subject to monitoring that must be dispensed with red prescription, green prescription and regular prescription is maintained; ç. A safety band should be added or d. The

outer packaging should be covered with a transparent additional outer packaging that does not obstruct the visibility and legibility of all labeling information; or e. Adhesive side tab should be used or f. Outer packaging with a dentelage cut (serrated or free- cut with various bevels) should be used so that it can be detected that the box has been opened.

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22. In order to facilitate the use of the medicinal product and to reduce the risks that may arise, a multimedia QR code may be added to the outer packaging and, if deemed necessary, to the additional instructions for use (IU) in accordance with the requirements of the Regulation on Promotional Activities for Medicinal Products for Human Use and taking into account the following points: g. Multimedia files linked to the multimedia QR code should be organized either as audio-only files or as audio, video and subtitles. ğ. The information contained in the multimedia files linked to the multimedia QR code must comply with the current approved IU information for the product and must not contain any information other than that contained in the IU. In this regard, a commitment must be submitted by the license holder companies that "the content of the multimedia QR code does not contain any information other than the information contained in the IU". h. Multimedia files linked to the multimedia QR code may also contain "additional risk minimization materials" approved by the Agency and prepared for patients. ı. Following the approval of the updates to the IU by the Agency, the multimedia files linked to the multimedia QR code should also be updated. i. The multimedia QR code to be applied on the packaging / IU must be in a size and position that does not interfere with the readability of other product information. j. The multimedia QR code symbol must be accompanied by the phrase "Scan code for information media." k. For products with a multimedia QR code on the outer packaging, the IU should include the statement "You can access detailed and up-to-date information about this medicine by scanning the QR code with a smartphone/tablet or a QR code reader".

Evaluation of Packaging Information and Instructions for Use

The proposed internal and external packaging and instructions for use are examined for compliance with the conditions specified in the Regulation. The Agency also carries out a general check on the packaging sample 3 for readability to contribute to the safe use of medicinal products for human use (e.g., packaging design, fonts and font sizes, separation between duplicates, etc.).

Changes to Packaging Information and Instructions for Use

The applicant/license/permit holder must first submit to the Agency any changes to the packaging information or instructions for use that are not covered by the short product information. If the change in the packaging information or the instructions for use is part of a variation, the change shall be dealt with in accordance with the requirements of the relevant variation, provided that only the area affected by the relevant variation is changed in the most recently approved packaging information or instructions for use. Approval of the proposed variation means that only the relevant field in the packaging information or instructions for use is approved.

3 The packaging sample is a copy of the two- dimensional drawing in full color, which, after cutting and folding when necessary, presents a copy of the immediate and outer packaging in a way as to ensure that the three- dimensional presentation of the packaging information text prepared with the information subject to license/permit is clear.

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Packaging Design

In order to avoid the risk of confusion and error, product packaging that is similar in name, pharmaceutical form and presentation, but different in loss, should provide clear color and/or size differences where necessary.

SECTION 2

Purpose

Main purpose of this document is to provide guidance on ensuring that the information on the packaging and instructions for use is clear so that medicinal products for human use can be used safely and appropriately. This manual also contains information on how to fulfill the requirements for the braille format.

Readability of Packaging Information and Instructions for Use

1. Recommendations on Packaging Information

l. Packaging information covers both outer and inner packaging. m. The following sections should be taken into account before the design of the packaging information is submitted to the Agency.

1.1. Print Size and Type

n. The packaging information of all medicinal products for human use must be written in at least 7-font characters (or in a size where the height of the "x" in lower case is at least 1.4 mm) with sufficient space between the lines to be readable. o. The text containing the information presented, especially in small packages, should be carefully drafted to ensure that it is presented in as large a font size as possible to reduce the likelihood of medication errors. ö. Among the issues included in the Regulation, especially the name of the medicinal product for human use, its availability and, where applicable, its total content and route of administration are considered critical for the safe use of the medicinal product for human use. Where possible, they should be combined in the packaging information using a sufficiently large font size. To assist users, care should be taken to ensure that this information is in the same field of view on the packaging. p. Information on the inner and outer packaging must be written with moisture-proof paint.

1.2. Organization and Design of Information

r. Applicants/license/permit holders should make the best use of space to ensure that important information is clearly indicated on the inner and outer packaging in an adequately sized font. s. Emphasis should be placed on the spacing between lines and the use of white space to increase the readability of the information presented. For some small packages it may not be possible to present all information in the same field of view. It is recommended to use innovative techniques to assist packaging design in the identification and selection of medicinal products for human use, or where space is at a premium.

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ş. Colors should be chosen to provide a good contrast between text and background to ensure maximum readability and access to information. High-gloss, metallic or reflective packaging should be avoided as this will affect the readability of the packaging information. It is appropriate not to use different colors in the name of the medicinal product for human use, as this may adversely affect the correct identification of the name of the medicinal product for human use. The use of different colors is primarily recommended to facilitate the differentiation of different orphanages. t. Similarities in packaging information that may lead to misuse of medicines should be reduced through the appropriate use of colors in packaging. The number of colors used in packaging needs to be carefully considered, as too many colors can cause confusion. It is recommended that the color used on the outer packaging is also applied to the inner packaging to help identify the medicinal product for human use.

1.3. Blister Pack Presentations

u. In blister pack presentations, it is important that the details are visible to the user until the last dose is removed from the blister pocket. If possible, all information should be applied to each blister pocket; if not, the maximum possible space should be provided. In all cases, the batch number and expiry date must be written on the end of the blister strip. If technically feasible, this information should be written on both ends of the blister strip. If a blister presentation in the form of a unit dose is intended to be produced, all the information required for blister packs must be included in each unit dose presentation. ü. Furthermore, blister foils should be printed in a sufficiently large font to ensure the legibility of the information. v. The color and font style of the text should be carefully selected to ensure the legibility of the text on the blister foil. Where possible, non- reflective material or colored foils should be considered to enhance the readability of the information presented and to ensure correct identification of the medicinal product for human use.

1.4. Small Inner Packages

y. The criteria for inner packages that are too small to contain the features and information specified in the first paragraphs of Articles 5 and 9 of the Regulation in terms of packaging information apply to containers with a volume of 10 mL or less. z. Where space is available, innovative packaging designs are encouraged (e.g., wrap- around or accordion- like labels). For example, it is recommended to use moisture-proof paper labels to improve the readability of the information applied to the bulbs. aa. In addition, necessary precautions should be taken to ensure readability in colored bulbs. At this point, the font color and character should be chosen with readability in mind. For example; for amber colored bulbs, light colored text should be chosen instead of dark colored text.

1.5. Braille Printing

bb. Braille is an internationally widely used reading and writing system for blind and partially sighted people. The system was developed in 1825 by Louis Braille (1809- 1852), who lived in France and was himself blind. Braille is not a language but another way of reading and writing a language. Braille consists of a series of dots that form the letters of the alphabet, numbers, and punctuation marks. The basic Braille symbol is called a Braille cell. Due to the

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differences in Braille in different countries, the type of Braille letter (size of the Braille cell) needs to be standardized. The Marburg Medium sign group is particularly recommended. The unabridged Braille alphabet system should be used. In this system, each Braille character (Braille cell) forms the letters of the alphabet, punctuation marks, numbers, etc. The abbreviated Braille system with letter combinations should not be used, except for small volume (up to 10 mL) packages. cc. The name of the medicinal product for human use (the trade name of the medicinal product for human use invented in such a way as to avoid confusion with the common name of it, or the name of the license or permit holder of the medicinal product for human use, or the common or scientific name given together with the trademark) and its strength must be respectively indicated in Braille on the outer packaging of the medicinal product for human use. Other information (pharmaceutical form and, where applicable, information on whether it is intended for infants, children or adults) It can be specified in Braille. It is also recommended to indicate the expiry date in Braille, although it is recognized that this may be impractical. çç. For small- volume packages (up to 10 mL) and for larger-volume packages where the full name of the medicinal product for human use and its identity cannot be accommodated, alternative ways of presenting information in Braille may be considered, for example, the use of abbreviated Braille or some defined abbreviations. Particular attention should be paid to medicinal products that are likely to be used by a target population with highly impaired vision (such as certain eye drop preparations). Products intended to be administered only by healthcare professionals (including

those available at pharmacies) do not need to have the name in Braille on the packaging; for example, vaccines, radiopharmaceuticals, hospital products, etc. do not need to have the name in Braille. dd. For herbal medicinal products, the Braille requirement applies only to the trade name of the herbal medicinal product. When the trade name consists of the active substance(s), the information required may be limited to the plant name (+ plant parts from which the active substance is derived where several parts are available), the part of the preparation where several parts are available and the pharmaceutical form. ee. The name in Braille does not have to be printed on the inner packaging - for example, on blisters, ampoules and vials, it only needs to appear on the outer packaging, which is usually cardboard. In the absence of outer packaging, e.g., for large volume bottles (500 mL, 1000 mL, etc.), an adhesive moisture-proof label in Braille can be attached around the bottle during the production process. Braille may not be applicable for plastic drip bags. ff. The applicant/license/permit holder may include the name in Braille on all packaging components. Braille text does not have to be placed on the outer packaging in the empty space of the packaging, but should ensure that the printed text on the bottom is easily readable.

2. Recommendations for Instructions for Use

Instructions for use are intended for patients/users. It is important that the instructions for use are well designed and clearly written, especially for people with low literacy skills and a certain degree of visual impairment.

2.1. Font and Font Size

gg. Choose a font that is easy to read. For example, a font in which similar letters/numbers such as "i", "l" and "1" can be easily distinguished from each other should be chosen.

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ğğ. The font size should be large enough to help readers. The information in the instructions for use must be printed in 'Times New Roman' font, as measured, in a non-contracted font size of at least 8 points, with sufficient space between the lines to make them legible. In cases where the instructions for use cannot be used in the outer packaging of the medicinal product for human use or in the inner packaging or in the outer packaging, the size of the text may be re-evaluated by the Agency, provided that justification is provided. hh. Different text sizes (e.g., for headings) should be used to increase the visibility of key information and to make it easier to find information in the text. ii. Larger font sizes may be used if the medicinal product for human use is intended for a patient group that is likely to have visual impairment. ii. Capital letters should not be used extensively. Since the human brain perceives words in written documents in the form of words, it is preferable to use lowercase text for long blocks of text. However, capital letters can be useful for emphasis. jj. Italic font style and underlining should not be used except where necessary, as it makes it difficult for the reader to perceive the word shape, except as specified in the text of the Standard Evaluation Procedure (SDP) of the Instructions for Use. However, the italic font style is applicable when using Latin terms.

2.2. Organization and Design of Information

- "Justified" text (text that justifies to both the left and right margins) should not be used.
- Line spacing should be clear. The space between lines is an important factor affecting the clarity of the text. As a general rule, whenever possible, the space between two lines should be at least 1.5 times greater than the space between words on one line.
- Contrast between text and background is important. The weight of the paper, the color of the paper, the size and weight of the font, its color and the paper itself should be taken into account. Low contrast between text and background negatively affects the accessibility of information. Therefore, if images are used on the background, they should not be placed behind the text, as they can affect the clarity of the text, making it difficult to read.
- The column format for text can help the reader navigate the page. The margins between columns should be large enough to adequately separate the text. If space is limited, a vertical line can be used to separate the text. Relevant information needs to be kept together so that text flows easily from one column to another. A landscape layout can be used, which can help patients.

2.3. Headings

- Headings can help patients navigate the text. Therefore, bold or different colored fonts for the heading can make this information stand out. Spacing above and below headings must be applied consistently throughout the Instructions for Use. To assist the reader, headings (numbering, bullet points, color, indentation, font and size) should be used consistently at the same level.
- Headings on more than one level should be used with caution, as more than two levels can make the instructions for use difficult to read.
- The use of line spacing to separate different sections within the text can also help as an orientation tool.

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- All main section headings specified in the Regulation must be included in the instructions for use. The current Instructions for Use published by the institution must be prepared in accordance with the SDP.

2.4. Print Color

- Not only the print size determines the accessibility of the information in the instructions for use. Fonts can be printed in one or several colors and thus clearly distinguishable from the background. A different font or color is one way to make headings and other important information clearly noticeable.
- The relationship between the colors used is as important as the colors themselves. As a general rule, dark text should be printed on a light background. However, the use of inverted colors (light text on a dark background) can be considered, for example, to highlight some warnings. In such cases, the quality of the print needs to be carefully assessed and it may be necessary to use a large font or bold text. Similar colors should not be used for text and background as readability may be impaired.

2.5. Syntax

- Some people may have poor reading skills, while others may lack health knowledge. Try to use simple words of a few syllables and avoid long sentences.
- Long paragraphs can confuse readers, especially where side effects are listed. It would be more appropriate to use bullet points for such lists. Whenever possible, it is recommended to use no more than five or six bullet points in a list.
- In general, it is advisable to indicate side effects according to the frequency of occurrence, starting with the most common, to help communicate the level of risk to individuals. According to the text of the SDP of the package leaflet, side effects may also be given in terms of severity where necessary. Frequency terms should be explained in a way that patients/users can understand - for example, "very common" (more than 1 in 10 patients). However, if there is a serious side effect that requires urgent action by the patient/user, more attention should be paid to this and it should be indicated at the beginning of the section. It is not recommended to specify side effects by organ/system/class, as patients/users are often not familiar with these classifications.

2.6. Style of Expression

- An active rather than passive style of expression should be used in the articles. For example:

- 'Take 2 tablets' instead of '2 tablets should be taken'.
- 'You must ...' instead of '... is a must'.

- The reasons for this should be presented when indicating what measures patients will take. The instruction should be presented first, followed by the relevant justification. For example: 'be careful taking X if you have asthma - its use can cause an attack'.
- Phrases such as "your medicine, this medicine" should be used instead of repeating the name of the product, as long as it is clear what is being referred to.

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- Abbreviations and short names should not be used unless they are inappropriate. When used for the first time in the text, their meaning should be fully specified. Similarly, scientific symbols (e.g., > or <) should not be used unless necessary because they are not well understood.
- Medical terms should be translated into a language that patients can understand. The colloquial definition should be preceded by an explanation and followed by the detailed medical term to ensure consistency in translations. The most appropriate (colloquial or medical) term may then be used throughout the instructions for use, depending on the situation. Ensure that the language used alerts the reader to all the information that is important to them and provides sufficient detail on how to recognize possible side effects and understand the precautions that may be required.

2.7. Paper

- The paper chosen should be thick enough as transparency can make reading difficult, especially when the text size is small. Uncoated paper should be preferred as glossy paper reflects light and makes information difficult to read.
- When the instructions for use are folded, make sure that the folds do not interfere with the readability of the information.

2.8. Use of Symbols and Pictorial Diagrams

Symbols and pictorial diagrams to be used under the Regulation may be useful as long as the meaning of the symbol is clear and/or the size of the graphic makes it easy to read. They should only be used to help orientation, to clarify or emphasize some aspect of the text and should not replace the text itself. Evidence may be required to show that their meaning is generally understood and not misleading or confusing. If there is any doubt about the meaning of a particular pictorial diagram, that pictorial diagram will be considered inappropriate.

2.9. Additional Information

2.9.1. Product Types

- There should be a separate package leaflet for each product and pharmaceutical form of the medicinal product for human use. However, on a product-by-product basis, the Agency may decide to authorize the use of combined instructions for use for different strengths and/or different pharmaceutical forms (e.g., tablets and capsules), for example if a recommended dose requires a combination of different strengths or if the dose varies from day to day according to the clinical response.
- If necessary for treatment, other preparations and pharmaceutical forms of the same medicinal product for human use may be indicated. For example, a reference may be made to a different orphanage, or the instructions for use of a tablet that is not suitable for children may state that an oral solution for children is available without using the trade name.

2.9.2. Products Administered by a Healthcare Professional or in a Hospital

- For a medicinal product for human use administered by a healthcare professional, information from the brief product information for healthcare professionals may be included at the end of the package leaflet, for example in a tear-off section, to be removed before giving it to the patient. Alternatively, the full brief product information can be included in the package with the instructions for use.

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- For a medicinal product for human use administered in a hospital, additional instructions for use may be provided upon request (in addition to the package leaflet) to ensure that each patient receiving the medicinal product for human use has access to the information.

2.10. Templates for Instructions for Use

The current Instructions for Use published by the Agency are included in the SDP.

2.11. Instructions for Use for the Visually Impaired and Partially Sighted

For partially sighted and visually impaired people, the text should be presented in an appropriate format. Except for products intended to be administered only by healthcare professionals (including those obtained from pharmacies, e.g. vaccines, radiopharmaceuticals, hospital products, those that fall within the scope of small packaging in accordance with the Regulation on Packaging Information, Instructions for Use and Follow-up of Medicinal Products for Human Use, etc.), the outer packaging may contain a QR code prepared in accordance with the requirements of the Regulation on Promotional Activities for Medicinal Products for Human Use, including a link to the audio file of the instructions for use. In order to indicate the location of the QR code on the outer packaging, it can be positioned so that the "QR" letters are located above the QR code containing the audio IU in Braille. The QR code in question may be in the content of the multimedia QR code on the outer packaging mentioned in Section 1, Article 22 of this manual, or it may be a QR code independent of the multimedia QR code in question. After updating the instructions for use, the text of the instructions for use on the QR code must also be updated within 30 days.

Additionally:

- If the applicant requests the inclusion of instructions for partially sighted persons, an IU should be submitted in an appropriate font and size, taking into account all aspects of readability (e.g., font and font size: 16- 20; contrast: black letters on white paper; spacing between words; alignment of text; spacing between lines; paper quality).
- For the visually impaired, the instructions for use can be presented in Braille.
- The package leaflet for the visually impaired should start with the statement "The IU of this medicinal product for human use was updated on ... and the current IU is given below." and the date of the update of the IU should be indicated.

2.11/A Electronic Instructions for Use (e- IU)

- For all other medicinal products for human use, except for products intended to be administered only by healthcare professionals (including those supplied from pharmacies, e.g.

vaccines, radiopharmaceuticals, hospital products) those that fall within the scope of small packaging and products without outer packaging in accordance with the Regulation on Packaging Information, Instructions for Use and Follow-up of Medicinal Products for Human Use, it is mandatory to have electronic instructions for use and printed instructions for use in the packaging at the same time. It is not suitable to have e-IU alone without printed instructions for use in the package information. e-The following points should be considered in the e-IU application: 1-e-IU will be accessed via a QR code on the outer packaging, the QR code in question may be in the content of the multimedia QR code on the outer packaging mentioned in Section

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1, Article 22 of this manual, or it may be a QR code independent of the multimedia QR code in question. 2-The information contained in the e-IU must be in line with the current IU and in cases where the IU needs to be updated, the e-IU must be updated within 30 days of the approval of the updated instructions for use. 3-The QR code to be applied on the packaging must be in a size and position that does not interfere with the readability of other product information. 4-The QR code symbol must be accompanied by the phrase "Scan code for information media." 5-For products with a QR code on the outer packaging, the IU should include the statement "You can access detailed and up-to-date information about this medicine by scanning the QR code with a smartphone/tablet or a QR code reader". 6-It must be possible to access the e-IU by scanning a single QR code using the device camera without the need for any additional software to be installed on the device where the QR code will be scanned. 7-No permission other than the KVKK should be required when accessing the e-IU on the device where the QR code will be scanned. 8-The e-IU may be in PDF format or may consist of HTML code. The entire IU should not be in a single image format (such as jpg, png). 9-MA holder companies must provide a commitment that the information contained in the e-IU is the same as the approved, up- to-date IU information for the product. 10-The website where the e- IU will be accessible must be active before the application is made to the Agency.

2.12. Readability Test

The instructions for use should be amended based on the results of consultation with the target patient groups to ensure that the instructions for use are easily readable and clearly understandable.

• An example of a method that can be used to test the readability of the Instructions for Use is presented below:

Objectives:

- Not simply confirming what is good, but finding out what is wrong with the instructions for use, - Ensuring that at least 16 out of 20 patients can answer each question correctly. • However, it is not necessary that the same 16 people answer each question correctly. It may be necessary to repeat the test several times to achieve this level of performance.

What kind of test?

The diagnostic test is the most useful and includes the following: - Asking users to do what they normally do when using the instructions for use, - Observing and recording what they do, - Examine whether they use the information they can read in an appropriate way, - Noting what they say about the instructions for use. • Diagnostic testing is often used where readability is a critical consideration. It is cheaper than more traditional methods such as surveys and focus groups and the resulting data is satisfactory.

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Who should administer the test?

It is best if the person who prepares the instructions for use does so. The preparer will benefit from the experience of test implementation and then apply them directly to their next job.

Who should be tested?

- The people tested must be from the population(s) at risk. Those most likely to have problems using the medicinal product for human use, for example elderly patients who are known to have had problems using medicines on many occasions should be included.
- It is not necessary to test people who have the disease treated by the medicinal product for human use. For the most part, participants who can reasonably assume that they may need to use this medicine in the future will suffice. This is especially so for more common diseases. However, if the medicine is for a rare disease or for a long period of time that requires some degree of patient knowledge, then it is better to test the instructions for use on those who actually have the disease.
- The inclusion of close-knit communities such as coworkers should be avoided. Such people can guide test questions, they can be used to check that the questions are getting the kind of answers expected.

What will be tested?

- The instructions for use must be in order and on the same paper when presented to patients.
- There are two questions: Can patients find the information in the instructions for use quickly and easily? And when they find the information, are they able to understand and act appropriately?

The testing procedure is as follows:

1. There is a set of tasks that are important for appropriate use and are specified in the instructions for use of each medicinal product for human use. This differs from one product to another. The critical areas of a leaflet are mostly "What is it used for?", "How is it used?" and "Possible side effects". The number of tasks (in the form of questions) selected for patients to perform using the Instructions for Use should normally not exceed 15. It is not practical or necessary to test every job as many are considered too simple or of low importance.
2. The questions should be organized as a single document.
3. Preferably, 10 patients should be included, especially people who are likely to have problems with this product (e.g., elderly patients).
4. One patient at a time should be tested and at least half an hour should be allocated to each person. Multiple instructions for use can be tested on each participant. For example, two short and relatively simple instructions for use can be tested. However, tests lasting more than 45 minutes may not be useful because participants will start to get tired.

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5. The order in which the questions are asked should be randomized, and two questions that point to similar information should not be asked in sequence. When asking each question, it is necessary to observe how patients use the instructions for use, how they search for information. To test the construct, it is necessary to pay attention to how people try to deal with the problem when they are confused or distracted.
6. When patients find information about what they are being asked, they will probably just read it. They should be asked to put the information into their own words and explain what is meant. This will reveal whether they understand what is written. If the question involves the description of a procedure, such as the use of an inhaler, they should be given a placebo inhaler and asked to perform the procedure in the order given in the instructions for use. An alternative is to ask them to describe the procedure themselves. The main goal, it must be remembered, is to try to find out not only what is understood but also what is misunderstood. Sometimes patients ask what it means when they find it difficult to understand something. It is important to avoid giving an answer, and to avoid questions such as "What do you think it means?" or "What do you normally understand when you read this?".
7. Once these 10 patients have been tested, the data should be reviewed. If there is a significant error in the instructions for use, some patterns may occur after this number of tests. This may provide sufficient data to rewrite parts of the instructions for use without additional testing.
8. After 10 patients have been tested with satisfactory data, an additional 10 people should be tested. The target is to ensure that at least 16 out of 20 patients can answer each question correctly. However, it is not necessary for the same 16 people to answer every question correctly. It may be necessary to modify the Instructions for Use and then retest several times to achieve this level of performance.

SECTION 3

EXCIPIENTS ON THE PACKAGING INFORMATION AND INSTRUCTIONS FOR USE OF MEDICINAL PRODUCTS FOR HUMAN USE

Purpose

This section is for applicants/license/permit holders. The annex contains excipients that must be specified in the packaging information of medicinal products for human use and outlines the information required in the instructions for use for excipients.

The provisions of this guideline do not apply to excipients included in this guideline when they are used as active substances.

Definitions and Examples

• Excipients include:

- Colorants, preservatives, adjuvants, stabilizers, thickeners, emulsifiers, sweeteners, aromatic substances, etc.
- Components of the outer coating of medicinal products for human use (capsules, gelatin capsules, rectal capsules, etc.) that are ingested or administered to the patient

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- Additional examples could be:

- Mixtures of excipients, e.g., for direct printing or for use in film coating or for polishing a dosage form for ingestion
- pH adjusters
- Printing ink components used to indicate the dosage form to be ingested
- Diluents such as plant extracts or vitamin concentrates
- Substances in a mixture of chemically related components (e.g., preservatives)

• However, residues, impurities, residual solvents, degradation products, etc. arising from the production process are not included in this definition. • Excipients are generally considered 'inert'. While it is desirable that excipients have little or no pharmacological effect on their own, some are known to have a known effect in certain circumstances. Therefore, applicants/license/permit holders should ensure that excipients in the formulation of medicinal products for human use are used in accordance with the information in Annex 1.

Terminology

The following information applies to the names of all excipients in the packaging information, instructions for use and brief product information:

1. Proprietary names should not be used for every excipient. For excipients, common names should be used or, if not possible, European Pharmacopoeia names.
2. The names of the excipients in Annex- 1 must be written with the "E" number if available. Since the package leaflet contains the full name of the excipients and the "E" number, if available, only the "E" number for the excipients can be given in the package information, since a complete qualitative composition is given in the instructions for use.
3. Taste and odorants that are proprietary can be described in general terms (e.g., "orange taste", "citrus smell"). Any known main ingredient or substances with a known effect in proprietary flavors and fragrances must be specifically identified.
4. Chemically modified excipients should be indicated in a way that does not cause confusion with unmodified excipients (e.g., pregelatinized starch).
5. pH adjusters must be specified by name; their function can also be specified (e.g. hydrochloric acid as pH adjuster).
6. All components of the mixture, including excipients, must be listed under general descriptive phrases (e.g., printing ink containing x, y, z). A general descriptive term may be used on the packaging as more information will be provided in the instructions for use. Each ingredient with a known effect must be indicated in the packaging information.

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Example: If the Opadry coating material contains any of the excipients with a known effect listed in Annex 1 at or above the threshold value, this should be indicated on the packaging.

Excipients in the Packaging Information

- According to the Regulation on Packaging Information, Instructions for Use and Follow-up of Medicinal Products for Human Use, all excipients in parenteral, ophthalmic and topical preparations must be listed on the packaging. Topical medicinal products;

- Those applied externally to the skin, - Respiratory system products transported to the lungs by inhalation - Medicinal products that are administered orally, nasally, rectally or vaginally and where the delivery is local or transdermal can be addressed in a comprehensive way.
- For all other medicinal products for human use, only excipients with a known effect need to be mentioned by name in the packaging information. These excipients are listed in Annex 1.
- If the medicinal product for human use contains any of the excipients listed in Annex- 1, the name of the excipient must be indicated on the package insert with the phrase "see the package leaflet for additional information".

Excipients in the Instructions for Use

- Excipients must be named in the instructions for use. All excipients must therefore be specified according to the terminology defined in this manual, as described above under Definitions and Examples.
- In line with what is stated in the sixth subparagraph of subparagraph c of the first paragraph of Article 8 of the Regulation on Packaging Information, Instructions for Use and Follow-up of Medicinal Products for Human Use, column 4 of the list in Annex- 1 provides clear and understandable information for the patient corresponding to each excipient. Taking into account that the wording in the text containing this information may be the specific wording of the application/permit/permit holder for the instructions for use, it is not necessary to follow the wording in the list in Annex- 1 verbatim in the instructions for use. Therefore, applicants/license/permit holders may present information in their own unique wording, provided that the content or meaning of the text does not change and is understandable to the patient.
- If a warning or disclosure of information is required according to the list in Annex 1, the relevance of this warning or disclosure to the excipient must be clearly stated in the instructions for use and short product information. Patients should not be left in any doubt as to whether the warnings are for the excipient or the active substance.
- For some excipients listed in Annex 1, the information in the package leaflet may relate to more than one section of the package leaflet; for example, the effect on the ability to operate machinery, pregnancy and breastfeeding, undesirable effects. To simplify the instructions for use, this information should only be mentioned once. It may be necessary to refer to the excipient warnings in other sections of the package leaflet so that the patient does not miss important information. For ethanol, for example, it may be necessary to refer to the excipient warnings in the sections of the package leaflet on the effect on driving, pregnancy and breastfeeding, information for children, etc.

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SECTION 4

MISCELLANEOUS AND FINAL PROVISIONS

REPEALED GUIDELINE • The "Guideline on Readability of Packaging and Instructions for Use of Medicinal Products for Human Use" published in February 2008 has been repealed. • The "Guideline on Excipients in the Packaging and Patient Instructions for Use of Medicinal Products for Human Use" published in June 2005 was repealed.

ATTRIBUTIONS

• References to the Guideline on Readability of Packaging and Instructions for Use of Medicinal Products for Human Use published in February 2008 and the Guideline on Excipients in Packaging and Instructions for Use of Medicinal Products for Human Use published in June 2005 shall be deemed to be references to these Guidelines.

ENFORCEMENT

- This Guideline shall enter into force on the date of issuance.

EXECUTION

• The provisions of this Guideline shall be executed by the Head of Turkish Medicines and Medical Devices Agency.

ANNEX- 1: Information for Excipients and Instructions for Use

Explanatory Notes

Name

INN, including a reference to the "E" number where relevant, or the name of the excipient using the terminology of the European Pharmacopoeia where possible

Route of administration

Since the information to be included in the packaging information, instructions for use and short product information (SmPC) may depend on the route of administration, it is mandatory to indicate the route of administration. For example, the information on bronchospasm for benzalkonium chloride applies only when used by inhalation.

Threshold

• It is recognized that excipients are only effective when they exceed a certain 'dose'. • Unless otherwise stated, the threshold is expressed as "Maximum Daily Doses" of the excipient in question. • The threshold is a value, and if it is equal to or greater than this value, the information needs to be specified. • a 'zero' threshold means that the information is required to be provided in each case where the relevant excipient is present in the medicinal product for human use.

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• The information is presented in a simple way with clear and understandable narratives that the patient can easily understand. • The term 'each dose' is often used in the text to mean the dose of the medicinal product for human use. • Since doses can be highly variable, the applicant/license/permit holder should always take into account the maximum single dose of the medicinal product for human use as specified in section 4.2 of the SmPC. • For this reason, the information may sometimes include statements such as 'up to x mg dose per dose'. • If the pharmaceutical form is a solid dosage form such as tablets, capsules, suppositories, sachets containing powder, etc., it is more appropriate to indicate the quantity in each tablet, capsule, etc.

Explanations

This column does not contain information for patients. It is intended to provide additional information that may be useful for applicants/license/permit holders. In some cases, these explanations may be written in appropriate wording and given as a contraindication in the SmPC.

PROVISIONAL ARTICLE 1 - (1) The obligations specified in Article 17 of Section 1 of this guideline shall be applied as of 01/07/2025.

PROVISIONAL ARTICLE 2 - (1) The obligations set forth in Article 21 of Section 1 of this guideline shall be applied as of 01/07/2025 for red and green prescription drugs and 01/07/2026 for drugs subject to monitoring that must be dispensed with regular prescription.

PROVISIONAL ARTICLE 3 - (1) The obligations specified in Article 11/A of Section 2 of this guideline shall be applied as of 01/01/2027.

ENFORCEMENT

This Guideline enters into force upon the Authorization of the President of the Agency.

EXECUTION

The provisions of this Guideline shall be executed by the President of the Agency.

REVISION HISTORY

Revision No Revision Date Justification and Remarks 1 11.09.2017 2 02.10.2017 3 23.02.2018 4 18.12.2018 5 23.01.2019 6 18.04.2020 7 15.11.2022 The guideline format has been updated. 8 23.05.2023 Regarding the Guideline on Packaging Information and Instructions for Use of Medicinal Products for Human Use: -Name of Medicinal Product for Human Use, -8. License/Permit Holder -9. Name and Address of Production (Manufacturing) Place,

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-Evaluation of Packaging Information and Instructions for Use, -17. Symbols and Other Information under Article 9 of the Regulation on Packaging Information, Instructions for Use and Follow-up of Medicinal Products for Human Use, -Footer and Article 13 have been updated. 8 23.05.2023 Articles 21 and 22 have been added to the Guideline on Packaging Information and Instructions for Use of Medicinal Products for Human Use. 8 23.05.2023 The "2.11. Instructions for Use for the Visually Impaired and Partially Sighted" section of the Guideline on the Readability of Packaging Information and Instructions for Use of Medicinal Products for Human Use has been updated. 8 23.05.2023 ANNEX-2: First Level Active Substances ANNEX- 3: Second Level Active Substances ANNEX- 4: Third Level Active Substances Attached in tables. 8 23.05.2023 "Provisional Article 1" has been added. 9 28.07.2023 Regarding the Guideline on Packaging Information and Instructions for Use of Medicinal Products for Human Use: -17. Symbols and Other Information under Article 9 of the Regulation on Packaging Information, Instructions for Use and Follow-up of Medicinal Products for Human Use, -Articles 21 and 22 have been updated.

9 28.07.2023 The "2.11. Instructions for Use for the Visually Impaired and Partially Sighted" section of the Guideline on the Readability of Packaging Information and Instructions for Use of Medicinal Products for Human Use has been updated. 9 28.07.2023 "Provisional Article 1" has been updated. 9 28.07.2023 "Provisional Article 2" has been added. 9 28.07.2023 "Provisional Article 3" has been added. 9 28.07.2023 "Vericiguat" has been added to the first level active substance list. 9 28.07.2023 "Trepstinil sodium" has been added to the second level active substance list. 10 03.10.2023 "Olipudase alfa" has been added to the first level active substance list. 10 03.10.2023 "Caplacizumab" has been added to the first level active substance list. 11 26.02.2024 "Bromfenac" has been added to the first level active substance list. 11 26.02.2024 "Anifrolumab" has been added to the first level active substance list. 11 26.02.2024 "Remdesivir" has been added to the first level active substance list. 11 26.02.2024 "Spesolimab" has been added to the first level active substance list.

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11 26.02.2024 "Bimekizumab" has been added to the first level active substance list. 11 26.02.2024 "Binimetinib" has been added to the first level active substance list. 11 26.02.2024 "Ozanimod" has been added to the first level active substance list. 11 26.02.2024 "Asciminib" has been added to the first level active substance list. 11 26.02.2024 ATC codes in the active substance lists prepared for vehicle warning triangles have been updated. 11 26.02.2024 "Cabotegravir" has been added to the second level active substance list. 12 10.06.2024 The sub-heading of Name of Medicinal Product for Human Use under the heading of Packaging Information and Instructions for Use Specified in the Regulation of SECTION 1: GUIDANCE ON PACKAGING INFORMATION AND INSTRUCTIONS FOR USE OF MEDICINAL PRODUCTS FOR HUMAN USE has been updated. 12 10.06.2024 The sub-heading of Instructions for Use for the Visually Impaired and Partially Sighted under the heading of Readability of Packaging Information and Instructions for Use of SECTION 2: GUIDANCE ON READABILITY OF PACKAGING INFORMATION AND INSTRUCTIONS FOR U SE OF

MEDICINAL PRODUCTS FOR HUMAN USE has been updated. 12 10.06.2024 "Potassium para-aminobenzoate", '5-Aminolevulinic acid hydrochloride' and 'Anakinra' have been added to the first level active substance list. 12 10.06.2024 "Ponatinib hydrochloride", "Vasopressin", "Eribulin mesylate", "Fedratinib dihydrochloride monohydrate" and "Avalglucosidase alfa" have been added to the second level active substance list. 12 10.06.2024 "Elranatamab" and "Aflibersept" have been added to the third level active substance list. 13 18.09.2024 The sub-heading of Instructions for Use for the Visually Impaired and Partially Sighted under the heading of Readability of Packaging Information and Instructions for Use of SECTION 2: GUIDANCE ON READABILITY OF PACKAGING INFORMATION AND INSTRUCTIONS FOR USE OF MEDICINAL PRODUCTS FOR HUMAN USE has been updated. 13 18.09.2024 "Ibutilide fumarate" has been added to the first level active substance list. 13 18.09.2024 "Inclisiran" has been added to the first level active substance list. 13 18.09.2024 "Tirzepatide" has been added to the second level active substance list. 13 18.09.2024 ATC codes in the active substance lists prepared for vehicle warning triangles have been updated. 13 18.09.2024 "Trastuzumab deruxtecan" has been added to the second level active substance list. 14/07/2017

13 18.09.2024 The vehicle triangle addition for the active substance diclofenac with ATC code M02AA15 and ibuprofen with ATC code M02AA13 has been amended as "eye preparations only". 13 18.09.2024 "Neratinib maleate" has been added to the second level active substance list. 13 18.09.2024 "ANNEX-1: Instructions for use and information table for excipients" has been updated. 13 18.09.2024 ANNEX-1/A: Table of the list of fragrance allergens requiring labeling on cosmetics and detergent products in the European Union has been added. 13 18.09.2024 "Benralizumab" has been added to the first level active substance list. 13 18.09.2024 "Faricimab" has been added to the third level active substance list. 13 18.09.2024 "Delaflaxacin" has been added to the second level active substance list. 14 06.12.2024 "Memantine and donepezil combinations" has been added to the second level active substance list. 14 06.12.2024 "Rocuronium bromide" has been added to the third level active substance list. 14 06.12.2024 "Lidocaine" has been added to the second level active substance list. 14 06.12.2024 "Sorbitol" has been updated in ANNEX-1: Instructions for use and information table for excipients. 14 06.12.2024 The "2.11. Instructions for Use for the Visually Impaired and Partially Sighted" section of the Guideline on the Readability of Packaging Information and Instructions for Use of Medicinal Products for Human Use has been updated. 14 06.12.2024 2.11/A Electronic Instructions for Use section has been added. 14 06.12.2024 "Dexketoprofen/Thiocolchicoside" has been added to the first level active substance list. 14 06.12.2024 "Chlorpheniramine" has been added to the second level active substance list. 14 06.12.2024 The date "01/01/2025" in Provisional Article 1 has been amended as "01/07/2025". 14 06.12.2024 The date "01/01/2025" in the second provisional article has been amended as "01/07/2025" and the date "01/01/2026" has been amended as "01/07/2026". 14 06.12.2024 The expression "11" in Provisional Article 3 has been amended as "11/A". 14 06.12.2024 "Prefusion F antigen derived from RSV subgroup A and B" has been added to the first level active substance list. 15 10.11.2025 ANNEX-1: Table of Instructions for use and Information on Excipients has been updated. 15 10.11.2025 "Provisional Article 3" has been updated. 15 10.11.2025 2.11/A Electronic Instructions for Use has been updated. 15 10.11.2025 Table of Contents has been updated. 14/07/2017

15 10.11.2025 17. Symbols and Other Information under Article 9 of the Regulation on Packaging Information, Instructions for Use and Follow-up of Medicinal Products for Human Use section has been updated. 15 10.11.2025 Annex-2, Annex-3 and Annex-4 of the Guideline has been removed in order to be published on the official website of the Agency. 14/07/2017

ANNEX-1: Information patient information leaflet and excipients
Name Route of Administration Threshold Information for Patient Information Leaflet

Explanations Aprotinin Topical Zero May cause hypersensitivity or severe allergic reactions. The

topical route here refers to places with access to circulation (e.g. wounds, body cavities, etc.)

Arachite Oil (Peanut Oil) All of them Zero (Medicinal product for human use) contains arachid oil (peanut oil). Do not use this medicinal product if you are allergic to peanuts or soy. Purified arachid oil may contain peanut proteins. The European Pharmacopoeia Monograph does not include a test for residual protein.

SmPC: Contraindication

Aspartame (E951) Oral Zero This medicine contains x mg of aspartame per <dosing unit> <unit volume> <equivalent> to <x mg/<weight><volume>. Aspartame is a source of phenylalanine. It can be harmful for people with phenylketonuria, a rare genetic disorder in which phenylalanine accumulates in the body because it is not properly excreted. Aspartame is hydrolyzed in the gastrointestinal tract when taken orally. One of the main hydrolysis products is phenylalanine. Information to consider for SmPC: There are no clinical or non- clinical data to evaluate the use of aspartame in infants younger than 12 weeks. Azo Coloring Agents E.g.

E102, tartrazine Oral Zero May cause allergic reactions.

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E110, sunset yellow FCF E122, azorubin, carmoizin E123, amaranth (marigold) E124, ponceau 4R red, cochineal red A E151, glossy black BN, black PN

Peru Balsam Topical Zero May cause skin reactions.

Benzalkonium Chloride All of them Zero This medicine contains x mg of benzalkonium chloride per <dosing unit> <unit volume> <equivalent> to <x mg/<weight><volume>.

Ocular Zero Benzalkonium chloride can be absorbed by soft contact lenses and can change the color of contact lenses. Before using this medicine, you should remove contact lenses and put them in after 15 minutes. Benzalkonium chloride can cause eye irritation, especially if you have dry eye and corneal (the transparent layer at the front of the eye) diseases. If you experience abnormal sensation, stinging or pain in the eye after use, consult your doctor. According to the limited data available, there is no difference in the adverse event profile in children compared to adults.

In general, however, the eye in children reacts more strongly to a given stimulus than the eye in adults.

Benzalkonium chloride has been reported to cause eye irritation, dry eye symptoms and may affect the tear film and corneal surface. It should be used with caution in

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patients with dry eyes and in patients with weak corneas.

Patients should be monitored during long-term use. Nasal Zero Benzalkonium chloride may cause irritation or swelling in the nose, especially with prolonged use. Long-term use may cause edema of the nasal mucosa. Respiratory tract Zero Benzalkonium chloride can cause wheezing or breathing difficulties (bronchospasm), especially if you have asthma.

On the skin Zero Benzalkonium chloride may cause skin irritation.

If you are breastfeeding, do not apply this medicine on the breast because it may pass to the baby with the milk during breastfeeding. Use during pregnancy and breastfeeding is not expected to be associated with harmful effects to the mother because absorption through the skin is minimal.

Do not apply to mucosa. Oromucosal, rectal, vaginal

Zero Benzalkonium chloride may cause local irritation.

Benzoic acid and benzoates: For example, E210 benzoic acid E211 sodium benzoate E212 potassium benzoate All of them Zero This medicine contains x mg of benzoic acid/benzoate salt per <dosing unit> <unit volume> <equivalent> to <x mg/<weight><volume>.

Oral, parenteral Zero <Benzoic acid/benzoate salt> may increase the risk of jaundice in newborn babies (up to 4 weeks of age). An increase in bilirubinemia after separation from albumin can increase neonatal jaundice, which can lead to the development of

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kernictorus (accumulation of unconjugated bilirubin in brain tissue). Topical Zero <Benzoic acid/Benzoate salt> may cause local irritation. May cause non-immunologic immediate contact reactions, possibly by a cholinergic mechanism. Topical Zero <Benzoic acid/benzoate salt> may increase the risk of jaundice in newborn babies (up to 4 weeks of age). Absorption through the immature skin of newborns is important. Benzyl alcohol All of them Zero This medicine contains x mg of benzyl alcohol equivalent to x mg per <dosage unit> <unit volume> per <weight> <volume>.

Benzyl alcohol may cause allergic reactions. Benzyl alcohol elimination is variable; in small infants such as newborns and in individuals with alcohol dehydrogenase polymorphism, benzyl alcohol accumulates in the body and causes toxicity. Oral, parenteral Zero Benzyl alcohol has been associated with serious side effects, including breathing problems (gasping syndrome) in young children. Do not give to a newborn baby (up to 4 weeks of age).

Warnings should be added to the section on excipients in the IU and under the heading "Section 3: Different age groups - Use in children." Additionally, warnings should be added in bold and in a box under the heading "Section 2: Precautions to be Benzyl alcohol has been associated with serious side effects, including respiratory problems (gasping syndrome) in young children. The minimum level of benzyl alcohol at which toxicity may occur is unknown. It should not be used in newborns.

Regarding use in newborns, warnings should be added to the posology section of the SPC under the heading "Additional information on special populations -

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taken before using ...". Pediatric population." Additionally, warnings should be added in bold and in a box in section 4.4 of the SPC. Oral, parenteral Zero Do not use in young children (under 3 years of age) for longer than one week without the advice of your doctor or pharmacist.

Warnings should be added to the section on excipients in the IU and under the heading "Section 3: Different age groups - Use in children." Additionally, warnings should be added in bold and in a box under the heading "Section 2: Precautions to be taken before using ...". Increased risk in young children due to accumulation. Do not use in children under 3 years of age for more than one week due to possible accumulation.

Regarding use in newborns, warnings should be added to the posology section of the SPC under the heading "Additional information on special populations - Pediatric population." Additionally, warnings should be added in bold and in a box in section 4.4 of the SPC. Oral, parenteral Zero If you are pregnant or breastfeeding, consult your doctor or pharmacist for advice. This is because large amounts of benzyl alcohol can build up in your body and cause side effects (known as metabolic acidosis).

Warnings should be added to the section on excipients in the IU and under the heading "Section 3: Different age groups - Use in children." Additionally, warnings should be added in bold and in a box under Possible accumulation may cause metabolic acidosis during pregnancy and lactation. Your doctor should evaluate the benefit/risk of using it. Additionally, warnings should be added in bold and in a box in section 4.4 of the SPC.

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the heading "Section 2: Precautions to be taken before using ...". Oral, parenteral Zero If you have liver or kidney disease, consult your doctor or pharmacist. This is because large amounts of benzyl alcohol can accumulate in your body and cause side effects known as metabolic acidosis.

Warnings should be added to the section on excipients in the IU and under the heading "Section 3: Special use – Kidney/liver failure." Additionally, warnings should be added in bold and in a box under the heading "Section 2: Precautions to be taken before using ...". Large volumes should be used in persons with liver or kidney failure cautiously and only if necessary due to risk of accumulation and toxicity (metabolic acidosis).

Warnings should be added to the posology section of the SPC under the heading "Additional information on special populations – Kidney/liver failure." Additionally, warnings should be added in bold and in a box in section 4.4 of the SPC.

Topical Zero Benzyl alcohol may cause mild local irritation.

Bergamot oil Bergapten Topical Zero May increase sensitivity to UV light (natural and artificial sunlight).

Do not apply bergamot oil if it does not contain bergapten.

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Boric acid (and borates) All of them 1 mg B/day* Do not give to children under 2 years of age because this medicine contains boron and may reduce fertility in later life. *1 mg B (Boron) = 5.7 mg boric acid.

The amount of boron, which can lead to reduced fertility when exceeded, is as follows for each age group: Age Reliability limit < 2 years 1 mg B/day < 12 years 3 mg B/day <18 7 mg B/day age** ≥ 18 10 mg B/day age**

** This amount can also harm the unborn child. All of them 3 mg B/day* Do not give to children under 12 years of age because this medicine contains boron and may reduce fertility in later life. *1 mg B (Boron) = 5.7 mg boric acid.

The amount of boron, which can lead to reduced fertility when exceeded, is as follows for each age group: Age Reliability limit < 2 years 1 mg B/day < 12 years 3 mg B/day < 18 7 mg B/day age** ≥ 18 10 mg B/day age**

** This amount can also harm the unborn child.

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All of them 7 mg B/day* Do not give to children under 18 months because this medicine contains boron and may reduce fertility in later life. If you are pregnant, consult your doctor before using this medicine because it contains boron which can harm your baby. 1 mg B (Boron) = 5.7 mg boric acid.

The amount of boron, which can lead to reduced fertility when exceeded, is as follows for each age group: Age Reliability limit < 2 years 1 mg B/day < 12 years 3 mg B/day <18 7 mg B/day age** ≥ 18 10 mg B/day age** ** This amount can also harm the unborn child. Bronopol Topical Zero May cause local skin reactions (e.g. contact dermatitis).

Butyl hydroxyanisole (E320) Topical Zero May cause local skin reactions (e.g. contact dermatitis) or irritation on eyes and mucous membranes.

Butyl hydroxytoluene (E321) Topical Zero May cause local skin reactions (e.g. contact dermatitis) or irritation on eyes and mucous membranes.

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Cetosterail alcohol including cetyl alcohol Topical Zero May cause local skin reactions (e.g. contact dermatitis).

Chlorkresol Topikal, parenteral Zero May cause allergic reactions. Cyclodextrins For example; Alfadex Betadex (E 459) γ- cyclodextrin Sulfobutyl- ether-β- Cyclodextrin (SBE-β- CD) Hydroxypropyl betadex Randomly methylated β- cyclodexytrin (RM- β- CD) All of them 20 mg/kg/day This medicine contains x mg of cyclodexytrine per <dosing unit> <unit volume> <equivalent> to <x mg/<weight><volume>. Do not use in children under 2 years of age unless recommended by your doctor. Cyclodextrins are excipients that can affect the properties of the active ingredient and other medicines. The safety aspects of cyclodextrins were taken into account during product development and safety assessment and are clearly stated in the SmPC. There is insufficient information on the effects of cyclodextrins in children under 2 years of age. Therefore, risk/benefit for the patient should be considered on a case-by- case basis.

Based on animal studies and human experience, harmful effects of CDs are not expected at doses below 20 mg/kg/day. Oral 200 mg/kg/day Cyclodextrins can cause digestive problems such as diarrhea. High doses of cyclodextrins can cause reversible diarrhea and cecal enlargement in animals.

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Parenteral 200 mg/kg/day and for use for more than 2 weeks If you have kidney disease, consult your doctor before using this medicine. In children under 2 years of age, low glomerular

function may protect against renal toxicity but may result in high levels of cyclodextrin in the blood.

Cyclodextrin accumulation may occur in patients with moderate and severe renal impairment. Dimethyl sulfoxide Topical Zero It may irritate the skin. Ethanol Oral Parenteral Inhalation Zero This medicine contains x mg of alcohol (ethanol) equivalent to $\frac{x \text{ mg}}{\text{weight} \times \text{volume}} \times \frac{y\% \text{ w/w}}{v}$ in each dosing unit $\times$ unit volume. The $\frac{\text{dose}}{\text{volume}}$ of this medicine is equivalent to A ml of beer or B ml of wine. The small amount of alcohol in this medicine will not have a noticeable effect. Where ethanol is present as a processing agent (e.g. in tablet coating) or as an extraction solvent and is evaporated, there is no need to mention ethanol in patient information.

To calculate the equivalent volume of beer and wine, assume that beer has an ethanol content of 5% v/v (alcohol by volume, ABV), which is equivalent to 4% w/v, and wine 12.5% v/v or 10% w/v (the specific gravity of ethanol is estimated to be about 0.8).

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The volumes of beer and wine (A and B) should be rounded up to the next whole number. Oral Parenteral Inhalation 15 mg/kg per dose This medicine contains x mg of alcohol (ethanol) equivalent to $\frac{x \text{ mg}}{\text{weight} \times \text{volume}} \times \frac{y\% \text{ w/w}}{v}$ in each dosing unit $\times$ unit volume. The $\frac{\text{dose}}{\text{volume}}$ of this medicine is equivalent to A ml of beer or B ml of wine.

The amount of alcohol in this medicine is unlikely to have an effect in adults and adolescents and is unlikely to be noticeable in children. In young children, there may be some effects, for example feeling sleepy.

The alcohol in this medicine may change the effects of other medicines. Talk to your doctor or pharmacist if you are taking other medicines.

If you are pregnant or breast-feeding, talk to your doctor or pharmacist before taking this medicine. To calculate the equivalent volume of beer and wine, assume that beer has an ethanol content of 5% v/v (alcohol by volume, ABV), which is equivalent to 4% w/v, and wine 12.5% v/v or 10% w/v (the specific gravity of ethanol is estimated to be about 0.8). Where relevant, ethanol interactions should be indicated in the SmPC (section 4.5).

Recommendation for the information in the SmPC: One dose of this medicine administered (select the maximum dose)

(A child aged A and an adult weighing B kg or an adult weighing 70 kg) would result in an ethanol exposure of C mg/kg, which could result in an increase in blood alcohol concentration of approximately D mg/100 ml.

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If you are addicted to alcohol, talk to your doctor or pharmacist before taking this medicine. For comparison, for an adult drinking a glass of wine or 500 ml of beer, the BAC is likely to be around 50 mg/100 ml.

Co-administration with propylene glycol- or ethanol-containing drugs, for example, may lead to ethanol accumulation and may cause adverse effects, especially in young children with low or immature metabolic capacity.

When a dose is given over a long period of time (e.g. by slow infusion over several hours), the increase in BAC will be less and the effects of ethanol may be reduced. In such cases, the patient information leaflet and SmPC should contain a statement such as the following: Since this medicine is usually administered slowly over XX hours, the effects of alcohol may be reduced. Oral Parenteral Inhalation 75 mg/kg per dose This medicine contains x mg of alcohol (ethanol) equivalent to $\frac{x \text{ mg}}{\text{weight} \times \text{volume}} \times \frac{y\% \text{ w/w}}{v}$ in each dosing unit $\times$ unit volume. The $\frac{\text{dose}}{\text{volume}}$ of this medicine is equivalent to A ml of beer or B ml of wine. See comments above.

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The alcohol in this preparation is likely to affect children. These effects may include feeling sleepy and changes in behavior. It can also affect their ability to concentrate and participate in

physical activities. The amount of alcohol in this medicine may affect your ability to drive or operate machinery. This is because it can affect your judgment and how quickly you react. If you have epilepsy or liver problems, talk to your doctor or pharmacist before taking this medicine. The amount of alcohol in this medicine may change the effects of other medicines. Talk to your doctor or pharmacist if you are taking other medicines.

If you are pregnant or breastfeeding, talk to your doctor or pharmacist before taking this medicine.

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If you are addicted to alcohol, talk to your doctor or pharmacist before taking this medicine.

Cutaneous Zero This medicine contains x mg of alcohol (ethanol) equivalent to <x mg/<weight><volume>><(y% w/<w><v>> in each <dosing unit><unit volume>. The <dose><volume> of this medicine is equivalent to A ml of beer or B ml of wine.

May cause a burning sensation on damaged skin. In neonates (preterm and term newborn infants), high concentrations of ethanol can cause severe local reactions and systemic toxicity due to significant absorption through immature skin (especially under occlusion). If applicable, the relevant warning in the SmPC/PIL should be added. Depending on the product and the ethanol concentration, a "flammable" warning may be required. Consideration should be given to including warnings about use near open flames, lit cigarettes or certain appliances (e.g. hair dryers). Formaldehyde Topical Zero May cause local skin reactions (e.g. contact dermatitis).

Oral Zero May cause nausea and diarrhea.

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Fragrances containing allergens

(See. ANNEX-1/A) Topical Zero This medicine contains fragrance with <allergen(s)>*. Allergen(s) may cause allergic reactions. *< >:Fragrance allergens are listed in the annex.

In addition to allergic reactions in sensitized patients, non-sensitized patients may become sensitized. Benzyl alcohol is listed as one of 26 fragrance allergens but can also be used as an excipient. When used as an excipient, benzyl alcohol (with or without added fragrance) applies to the packaging information of this excipient. Fructose Oral Parenteral Zero This medicine contains x mg of fructose per <dosing unit> <unit volume> <equivalent> to <x mg/<weight><volume>. The additive effect of co- administration of products containing fructose (or sorbitol) and dietary fructose intake should be considered.

Oral Zero [If the medicine comes into contact with teeth (e.g. oral liquids, lozenges or chewable tablets) and is intended for long- term use:] Fructose can damage teeth. Oral products that are used frequently or for longer periods, e.g. for two weeks or more. Intravenous (IV) Zero You should not take this medicine if you (or your child) have hereditary fructose intolerance, a rare genetic disease. The body of patients with hereditary fructose intolerance cannot break down the fructose Patients with hereditary fructose intolerance should not be given this medicine except when necessary in extremely limited circumstances.

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contained in this medicine, which can cause serious side effects.

Tell your doctor before taking this medicine if you (or your child) have hereditary fructose intolerance or if your child cannot eat sugary foods or drink sugary beverages because they may feel sick, vomit or have nausea, stomach cramps or diarrhea. In infants and young children (under 2 years of age), inherited fructose intolerance may not be diagnosed. Intravenously administered drugs (containing fructose) can be life- threatening and should be contraindicated in this population unless there is a very strong clinical need and no other available alternative.

A detailed history of hereditary fructose intolerance symptoms should be taken from each patient before this medicine is given. Oral Parenteral (other than IV) 5 mg/kg/day If you (or your child) have previously been told by your doctor that you (or your child) have an intolerance to certain sugars, or if you (or your child) have been diagnosed with hereditary fructose intolerance, a rare genetic disorder in which glucose cannot be broken down by the body, contact your doctor

before you (or your child) take this medicine. Patients with hereditary fructose intolerance should not be given this medicine/should not take this medicine. Galactose Oral, Parenteral Zero If you have been previously told by your doctor that you are intolerant to certain sugars, contact your doctor before taking this medicinal product. SmPC recommendation: Patients with rare inherited galactose intolerance problems (e.g. galactosemia) or galactose malabsorption should not use this medicine.

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Oral Parenteral 5 g Each dose contains x g of galactose. This should be taken into account in diabetic patients.

Glucose Oral Zero If you have been previously told by your doctor that you are intolerant to certain sugars, contact your doctor before taking this medicinal product.

Patients with rare glucose-galactose malabsorption disease should not use this medicine. Oral Parenteral 5 g Each dose contains x g of glucose. It should be considered in diabetic patients.

Oral liquids, lozenges and chewable tablets Zero It can be harmful to teeth. It should only be indicated in the case of chronic use of the medicinal product, for example for two weeks or more.

Glycerol Oral 10 g/dose May cause headache, nausea and diarrhea.

Rectal 1 g May have a mild laxative effect.

Heparin (as excipient) Parenteral Zero May cause allergic reactions and lower blood cell counts, which can affect the blood clotting system. Patients with a history of heparin- induced allergic reactions should avoid heparin- containing medicines.

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Hydrogenated Glucose syrup (or liquid Maltitol) Oral Zero If you have been previously told by your doctor that you are intolerant to certain sugars, contact your doctor before taking this medicinal product. SmPC recommendation: Patients with rare inherited fructose intolerance problems should not use this medicine. Oral 10 g May have a mild laxative effect. The caloric value of hydrogenated glucose syrup is 2.3 kcal/g.

Invert sugar Oral Zero If you have been previously told by your doctor that you are intolerant to certain sugars, contact your doctor before taking this medicinal product. SmPC recommendation: Patients with rare inherited fructose intolerance problems (e.g. glucose-galactose malabsorption) should not use this medicine.

Oral 5 g Each dose contains x g of a mixture of fructose and glucose. It should be considered in diabetic patients.

Oral liquids, lozenges and chewable tablets Zero It can be harmful to teeth. It should only be indicated in the case of chronic use of the medicinal product, for example for two weeks or more.

Lactitol, E966 Oral Zero If you have been previously told by your doctor that you are intolerant to certain sugars, contact your doctor before taking this medicinal product. SmPC recommendation: Patients with rare inherited fructose intolerance, galactose intolerance or glucose-galactose malabsorption problems should not use this medicine.

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Oral 10 g May have a mild laxative effect. Caloric value is 2.1 kcal/g lactitol.

Lactose Oral Zero If you have been previously told by your doctor that you are intolerant to certain sugars, contact your doctor before taking this medicinal product. SmPC recommendation: Patients with rare inherited galactose intolerance, Lapp lactose insufficiency or glucose-galactose malabsorption problems should not use this medicine.

Oral 5 g Each dose contains x g of lactose (x/2 glucose and x/2 galactose). It should be considered in diabetic patients.

Lanolin (see Fleece oil) Topical Zero May cause local skin reactions (e.g. contact dermatitis).

Latex Natural Rubber (latex) All of them Zero The container of this medicinal product contains latex rubber. May cause severe allergic reactions.

It is not a typical excipient, but a warning is considered necessary. Macrogolglycerol Ricinoleate (polyoxyl castor oil) Macrogolglycerol Hydroxystearate (polyoxyl hydrogenated castor

oil) Parenteral Zero May cause severe allergic reactions.

Oral Zero May cause stomach upset and diarrhea.

Topical Zero May cause skin reactions.

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Maltitol E965 and Isomaltitol E953, liquid Maltitol (see Hydrogenated Glucose syrup) Oral Zero If you have been previously told by your doctor that you are not tolerant to certain sugars, contact your doctor before taking this medicinal product.

SmPC recommendation: Patients with rare inherited fructose intolerance problems should not use this medicine. Oral 10 g May have a mild laxative effect. The caloric value is 2.3 kcal/g maltitol (or isomaltitol).

Mannitol, E421 Oral 10 g May have a mild laxative effect.

Organic mercury compounds e.g. Thiomersal Phenylmercuric nitrate, acetate, borate Ocular Zero May cause allergic reactions.

Topical Zero May cause local skin reactions (e.g. contact dermatitis) and discoloration.

Parenteral Zero This medicinal product contains a preservative (thiomersal) and there is a possibility that "you and/or your child" may have an allergic reaction. Tell your doctor if "you and/or your child" have known allergic conditions.

Parenteral Zero Tell your doctor if "you and/or your child" have had health problems after a previous vaccination.

Additional explanations are provided for vaccinations. Parahydroxybenzoates and esters (Parabens) Oral Ocular Topical Zero May cause (possibly delayed) allergic reactions.

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e.g.

E214 Ethylhydroxybenzoate E216 Propylhydroxybenzoate E217 Sodium Propylhydroxybenzoate E218 Methylhydroxybenzoate E219 Sodium Methylhydroxybenzoate Parenteral Respiratory tract Zero May cause (possibly delayed) allergic reactions and exceptionally bronchospasm.

Phenylalanine All of them Zero This medicine contains x mg of phenylalanine per <dosing unit> <unit volume> <equivalent> to <x mg/<weight><volume>.

Phenylalanine can be harmful if you have phenylketonuria, a rare genetic disorder in which phenylalanine accumulates in the body because it is not properly excreted.

Phosphate buffers Ocular Zero This medicine contains x mg of phosphate per <dosing unit> <unit volume> <equivalent> to <x mg/<weight><volume>. If there is severe damage to the transparent layer in the front of your eye (cornea), phosphates can cause blurred patches in rare cases due to calcium build-up during treatment. The statement replacing the SmPC statement in section 4.8 (Undesirable effects): "Very rare cases of corneal calcification have been reported with the use of phosphate-containing eye drops in some patients with severely damaged corneas."

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Potassium Parenteral Less than 1 mmol per "dose" This medicinal product contains less than 1 mmol (39 mg) of potassium per "dose", i.e. it is essentially "potassium-free". Information on a threshold value based on the total amount of K⁺ in the medicinal product. Especially for products used in pediatric doses, prescribers should be informed and parents should be reassured about the low K⁺ level in the product.

Parenteral Oral 1 mmol per "dose" This medicinal product contains x mmol (or y mg) of potassium in each "dose". This should be considered in patients with reduced renal function or in patients on a controlled potassium diet.

Intravenous 30 mmol/L May cause pain at the injection site.

Propylene glycol (E 1520) and esters All of them 1 mg/kg/day This medicine contains x mg of propylene glycol per <dosing unit> <unit volume> <equivalent> to <x mg/<weight><volume>.

Oral Parenteral 1 mg/kg/day If your baby is less than 4 weeks old, contact your doctor or pharmacist before giving this medicine, especially if your baby is being given propylene glycol or

other medicines containing alcohol. Co-administration with any substrate for alcohol dehydrogenases such as ethanol may cause serious adverse effects in newborns.

Oral Parenteral 50 mg/kg/day If your child is under 5 years of age, contact your doctor or pharmacist before giving this medicine, especially if your child is taking other medicines containing propylene glycol or alcohol. Co-administration with any substrate for alcohol dehydrogenases such as ethanol may cause serious adverse effects in children younger than 5 years.

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Oral Parenteral 50 mg/kg/day Do not use this medicine if you are pregnant or breastfeeding unless recommended by your doctor. Your doctor may do extra checks while you are taking this medicine. Although propylene glycol has not been shown to cause reproductive and developmental toxicity in animals and humans, it can pass to the fetus and has been found in breast milk. Consequently, the administration of propylene glycol to pregnant or breastfeeding patients should be considered on a case-by- case basis. Oral Parenteral 50 mg/kg/day Do not use this medicine if you have liver or kidney disease unless recommended by your doctor. Your doctor may do extra checks while you are taking this medicine. Patients with impaired renal or hepatic function should be medically monitored because several adverse effects such as renal dysfunction (acute tubular necrosis), acute renal failure or hepatic dysfunction have been associated with propylene glycol. Oral Parenteral 500 mg/kg/day The propylene glycol in this medicine has the same effects as drinking alcohol and increases the chance of side effects. Do not use this medicine in children under 5 years of age. Use this medicine only on doctor's advice. Your doctor may do extra checks while you are taking this medicine. Various adverse effects such as hyperosmolality, lactic acidosis; renal dysfunction (acute tubular necrosis), acute renal failure; cardiotoxicity (arrhythmia, hypotension); central nervous system disorders (depression, coma, seizures); respiratory depression, dyspnea; liver dysfunction; hemolytic reaction (intravascular hemolysis) and hemoglobinuria; or multisystem organ dysfunction have been reported with high doses or prolonged use of propylene glycol.

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Doses higher than 500 mg/kg/day may therefore be administered to children older than 5 years but should be evaluated on a case-by- case basis.

Adverse effects are usually reversed after discontinuation of propylene alcohol and in more severe cases this occurs after hemodialysis.

Medical monitoring is necessary. Cutaneous 50 mg/kg/day Propylene glycol may cause skin irritation.

Do not use this medicine in babies younger than 4 weeks with open wounds or extensive skin damage (such as burns) without consulting your doctor or pharmacist.

Cutaneous 500 mg/kg/day Propylene glycol may cause skin irritation.

Since this medicine contains propylene alcohol, do not apply to open wounds or skin with extensive damage without consulting your doctor or pharmacist.

Sesame oil All of them Zero May rarely cause serious allergic reactions. Sodium Oral, Parenteral Less than 1 mmol (23 mg) per dose This medicine contains less than 1 mmol sodium (23 mg) of sodium per <dosing unit><unit volume>, so it is actually "sodium-free". 1 mmol sodium (Na) = 23 mg Na = 58.4 mg salt (NaCl).

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This information relates to the threshold based on the total amount of sodium in the medicinal product.

This relates to products used in children and patients on what is essentially the lowest sodium diet to provide information for prescribers and reassurance to parents and patients interested in the low sodium level in the product. Oral, Parenteral 1 mmol (23 mg) per dose This medicine contains x mg of sodium (main food ingredient/table salt) per <dosing unit><unit volume>. This is equivalent to y% of the maximum recommended daily dietary sodium intake for adults. For parenterals with variable (e.g. weight-based) dosing, the sodium content may be

expressed in mg per vial. SmPC proposal: "This medicinal product contains x mg of sodium per <dosing unit><unit volume> equivalent to y% of the WHO recommended maximum daily intake of 2 g of sodium for adults."

Oral, Parenteral 17 mmol (391 mg) at maximum daily dose Contact your doctor or pharmacist if you need <Z> or more <dosage unit> daily for the long term, especially if you have been advised to follow a low salt diet. This applies to products where the labeled posology only allows the product to be taken daily for more than 1 month or with repeated use for more than 2 days each week.

17 mmol (391 mg) is approximately 20% of the WHO recommended

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maximum adult daily sodium intake of 2 g and is considered to represent a "high" level of sodium. This also applies to children, for whom the maximum daily intake is considered to be proportional to adults and based on energy requirements. <Z doses> indicates the lowest number of dosage units in which the sodium threshold of 17 mmol (391 mg) was reached/exceeded. Round to the nearest whole number. For the statement to be included in the SmPC, please refer to the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) recommendation: "1.3. Effervescent, dispersible and soluble sodium- containing medicinal products – Cardiovascular events" . (EMA/PRAC/234960/2015).

Sodium laurylsulfate Cutaneous Zero This medicine contains x mg of sodium laurylsulfate per <dosing unit> <unit volume> <equivalent> to <x mg/<weight><volume>.

Skin thickness varies greatly with age in relation to body area and can be an important factor in the case of sensitivity to sodium laurylsulfate (SLS).

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Sodium laurylsulfate may cause local skin reactions (such as stinging or burning sensation) or an increase in skin reactions caused by other products when applied to the same area.

Sensitivity to SLS will also vary by formulation type (and other excipient effects), SLS concentration, contact time and patient population (children, hydration level, skin color and disease).

Patient populations with reduced skin barrier function, such as in atopic dermatitis, are more sensitive to the irritant properties of SLS. Sorbic acid (E200) and its salts Topical Zero May cause local skin reactions (such as contact dermatitis).

Sorbitol (E420) Oral, parenteral Zero This medicine contains x mg of sorbitol per <dosing unit> <unit volume> <equivalent> to <x mg/<weight><volume>. The additive effect of co-administration of products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be considered.

The sorbitol content in medicinal products for oral use may affect the bioavailability of other medicinal products administered together for oral use.

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Intravenous (IV) Zero Sorbitol is a source of fructose. You should not take this medicine if you (or your child) have hereditary fructose intolerance, a rare genetic disease. The body of patients with HFI cannot break down the fructose in this medicine, which can cause serious side effects. Tell your doctor before taking this medicine if you (or your child) have hereditary fructose intolerance or if your child cannot eat sugary foods or drink sugary beverages because they may feel sick, vomit or have nausea, stomach cramps or diarrhea. Patients with hereditary fructose intolerance should not be given this medicine except when necessary in extremely limited circumstances. In infants and young children (under 2 years of age), inherited fructose intolerance may not be diagnosed. Intravenously administered drugs (containing fructose) can be life-threatening and should be contraindicated in this population unless there is a very strong clinical need and no other available alternative.

A detailed history of the symptoms of hereditary fructose intolerance should be taken from each patient before this medicine is given. Oral, parenteral (except for IV) 5 mg/kg/day Sorbitol is a

source of fructose. If you (or your child) have previously been told by your doctor that you (or your child) have an intolerance to certain sugars, or if you (or your child) have been diagnosed with hereditary fructose intolerance, a rare genetic disorder in which glucose cannot be broken down by the body, contact your doctor before you (or your child) take this medicine. Patients with hereditary fructose intolerance should not be given this medicine/should not take this medicine.

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Oral 140 mg/kg/day Sorbitol may cause gastrointestinal discomfort and a mild laxative effect.

Soybean oil (and hydrogenated soybean oil) All of them Zero (medicinal product) contains soybean oil. Do not use this medicinal product if you are allergic to peanuts or soy. SmPC in line with arachid oil: Contraindication Stearyl alcohol Topical Zero May cause local skin reactions (such as contact dermatitis).

Sucrose Oral Zero If you have been previously told by your doctor that you are intolerant to certain sugars, contact your doctor before taking this medicinal product. SmPC recommendation: Patients with rare hereditary fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase deficiency should not use this medicine.

Oral 5 g Each dose contains x g of sucrose. This should be considered in diabetic patients.

Oral liquids, lozenges and chewable tablets Zero It can be harmful to teeth. It should only be indicated in the case of chronic use of the medicinal product, for example for two weeks or more.

Sulfides including metasulfides For example: E220 sulfur dioxide E221 sodium sulfite Through Oral Parenteral Inhalation Zero May rarely cause severe hypersensitivity reactions and bronchospasm.

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E222 sodium bisulfite E223 sodium metabisulfite E224 potassium metabisulfite E228 potassium bisulfite

Wheat starch (containing gluten) Oral Zero This medicine contains only very low levels of gluten (from wheat starch) <. It is considered "gluten-free"* and is unlikely to cause problems if you have celiac disease. One <dosage unit> contains no more than x micrograms of gluten.

Patients allergic to wheat (other than celiac) should not use this medicinal product. [* "Gluten-free" only applies if the amount of gluten in the medicinal product is less than 20 ppm.] The name of the excipient on the package should be "Wheat starch". Xylitol (E967) Oral 10 g May have a mild laxative effect. The caloric value is 2.4 kcal/g xylitol.

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ANNEX- 1/A: List of fragrance allergens requiring labeling on cosmetic and detergent products in the European Union Substance CAS No 3-Methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-3-buten-2-one 127-51-5 Amyl cinnamal 122-40-7 Amylcinnamyl alcohol 101-85-9 Anisyl alcohol 105-13-5 Benzyl alcohol 100-51-6 Benzyl benzoate 120-51-4 Benzyl cinnamate 103-41-3 Benzyl salicylate 118-58-1 Cinnamal 104-55-2 Cinnamyl alcohol 104-54-1 Citral 5392-40-5 Citronellol 106-22-9 Coumarin 91-64-5 d-Limonene 5989-27-5 Eugenol 97-53-0 Farnesol 4602-84-0 Geraniol 106-24-1 Hexyl cinnamaldehyde 101-86-0 Hydroxycitronellal 107-75-5 Hydroxymethylpentyl-cyclohexenecarboxaldehyde 31906-04-4 Isoeugenol 97-54-1 Lilial 80-54-6 Linalool 78-70-6 Methyl heptin carbonate 111-12-6 Oakmoss 90028-68-5 Treemoss 90028-67-4