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Medicinal products for human use

Safety, environment and information

**Excipients in the labelling and package leaflet
of medicinal products for human use**

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EXCIPIENTS IN THE LABELLING AND PACKAGE LEAFLET OF MEDICINAL PRODUCTS FOR HUMAN USE

INTRODUCTION

In accordance with Article 65(e) of Directive 2001/83/EC¹ the Commission shall draw up detailed guidance with the list of excipients which must feature on the labelling of medicinal products and the way in which these excipients must be indicated. Therefore this guidance contains the warning statements relating to the presence of certain excipients in medicinal products above a threshold defined in the Annex. Homeopathic medicinal products authorised through a special simplified registration procedure require a specific labelling according to Article 69 of Directive 2001/83/EC. Although not addressed in this guideline, some of the information in the Annex may be used if relevant for these simplified procedures.

Article 54(d) requires that all excipients must appear on the outer packaging of medicinal products or, where there is no outer packaging, on the immediate packaging if the medicinal product is an injectable or a topical or eye preparation. Furthermore, for all other medicinal products, Article 54(d) provides that excipients known to have a recognised action or effect, and included in the guideline published by the Commission pursuant to Article 65(e), shall appear on the outer packaging or, where there is no outer packaging, on the immediate packaging.

Article 59(1)(f)(iv) requires the full qualitative composition (in active substances and excipients) and the quantitative composition in active substances to be included in the package leaflet. Article 59(1)(c) states that the package leaflet must include a list of information which is necessary before taking the medicinal product. Article 59(2)(c) provides that the aforementioned list of information shall list those excipients knowledge of which is important for the safe and effective use of the medicinal product and which are included in this guideline published pursuant to Article 65(e).

Article 59(1) requires that the package leaflet shall be drawn up in accordance with the Summary of the Product Characteristics (SmPC). Therefore, consistent information should be stated in both documents for all excipients listed in the Annex to this guideline.

PURPOSE

This guideline is for use by competent authorities, applicants for a Marketing Authorisation and Marketing Authorisation Holders. Its Annex provides a list of excipients which should be stated on the label and outlines the information for those which must appear on the package leaflet. This guideline does not apply to excipients when they are used as active substances.

DEFINITIONS AND EXAMPLES

In general, excipients are defined as any constituents of a medicinal product, other than the active substance and the packaging material.

According to Annex I of Directive 2001/83/EC, such constituents may include:

- colouring matter, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, flavouring and aromatic substances, etc.,
- the constituents intended to be ingested or otherwise administered to the patient, of the outer covering of the medicinal products (hard capsules, soft capsules, rectal capsules, coated tablets, film-coated tablets, etc.),

Further examples may include:

¹ DIRECTIVE 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67).

- transdermal patch constituents,
- excipient mixtures, e.g. those used for example in direct compression or in a film coat or polish for an ingested dose form, pH adjusters,
- the constituents of printing inks used to mark the ingested dose form,
- diluents present, for example in herbal extracts or vitamin concentrates,
- the constituents present in a mixture of chemically related components (e.g. preservatives).

However, in the context of this guideline, residues of substances arising from the manufacturing process, impurities, residual solvents, degradation products, etc. are not included in this definition.

In general, excipients are considered to be ‘inert’. Whilst it is desirable that excipients should have little or no pharmacological action of their own, some do indeed have a recognised action or effect in certain circumstances. Therefore Marketing Authorisation applicants and holders should ensure that excipients are used appropriately in the formulation of their medicinal products, with regard to the information contained in the Annex to this guideline.

NOMENCLATURE

The following applies to the names of all excipients on the labelling, package leaflet and the SmPC.

1. Proprietary names should not be used for individual excipients. Excipients should be referred to by their recommended international nonproprietary name (INN or INN modified (INN^M)) accompanied by the salt if relevant, or the European Pharmacopoeia name, their usual common name or failing this, the chemical name.
2. The name of an excipient appearing in the Annex to this guideline should be accompanied by the E number² if it exists. The E number alone may be used for an excipient on the labelling, provided that the full name and the E number are stated in the package leaflet.
3. Proprietary flavours or fragrances may be declared in general terms (e.g. ‘orange flavour’, ‘citrus fragrance/perfume’); any known major components or those with a recognised action or effect should be declared specifically.
4. For excipients which belong to a chemical group appearing in the Annex but are not explicitly listed (e.g. other salts, related chemical structure) the information for the package leaflet applies unless justified.
5. Chemically modified excipients should be declared in such a way as to avoid confusion with the unmodified excipient (e.g. pre-gelatinised starch).
6. pH adjusters should be mentioned by name and their function may also be stated in the package leaflet, e.g. hydrochloric acid for pH adjustment. The function should not be stated on the labelling.
7. All components of compound excipients or mixtures should be declared, listed under a general descriptive term e.g. printing ink containing x, y, z. A general descriptive term may be used on the labelling provided more information is given in the package leaflet. Any component with a recognised action or effect should be mentioned on the labelling.
8. Abbreviations for excipients should not be used. However, where justified for space considerations, abbreviations and/or latin names for excipients may appear on the labelling, on

² E number assigned to food additives in accordance with Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives (OJ L 354, 31.12.2008, p. 16).

condition that the full name of the excipients in the national language appears in the SmPC and the package leaflet.

EXCIPIENTS IN THE LABELLING

According to Directive 2001/83/EC, all excipients in parenteral, ocular and topical medicinal products must appear on the labelling (outer package or if no outer package on the immediate packaging). Topical medicinal products can be taken to include those medicinal products applied externally to the skin (including transdermal patches), respiratory products delivered to the lung by inhalation and any medicinal product delivered to the ear, oral, nasal, rectal or vaginal mucosae, i.e. where the delivery may be local or transdermal.

For all other medicinal products, only those excipients known to have a recognised action or effect, included in this guideline, should be declared on the labelling (outer package, or, if no outer package, on the immediate package). Such excipients are listed in the Annex.

When a medicinal product contains any of the excipients listed in the Annex, the name of the excipient and/or the E number where relevant, (e.g. for colourants) must be stated on the labelling, together with a statement such as 'see leaflet for further information'.

EXCIPIENTS IN THE PACKAGE LEAFLET

According to Article 59(1)(f)(iv) of Directive 2001/83/EC, all excipients must be stated on the package leaflet by name. Thus, all excipients, as indicated in the section on Definitions and Examples above, should be declared according to the nomenclature defined in this guideline.

In line with the provisions of Articles 59(1)(c)(iv) and 59(2)(c) of Directive 2001/83/EC, the fourth column (information for the package leaflet) in the Annex provides information corresponding to each excipient. The text of this information, written in clear and understandable terms for the patient, should be applied to the package leaflet by default. In some cases the applicant may adapt the style of the information if adequately justified (e.g. by means of user testing) as long as the information content and its meaning remain unchanged.

When a warning or information statement is required according to the Annex, it should be clear in the package leaflet and SmPC that the statement is linked to the presence of a particular excipient. The patient should not be left in any doubt as to whether the warning relates to the excipient or the active substance.

For some of the excipients in the Annex, the information to be included in the package leaflet may relate to more than one section of the leaflet, e.g. effects on ability to drive and operate machinery, pregnancy and lactation, undesirable effects, contra-indications, warnings and precautions. To simplify the presentation of the package leaflet, this information should appear only once. However, in order that the patient does not miss important and relevant information, it may be necessary to refer back to the excipient warnings section from other sections in the package leaflet. For example in the case of ethanol, it will be necessary to refer back to the excipient warnings section from those sections relating to effects on ability to drive, pregnancy and lactation, information for children, etc.

Note on the implementation of new statements for excipients listed in the Annex, as applicable

1) For new marketing authorisation applications, implementation of the information as per the latest revision of the guideline Annex should be followed.

2) For existing marketing authorisations granted before the publication of the revised Annex:

- Marketing authorisation holders (MAHs) are encouraged to use the first upcoming regulatory procedure affecting Product Information Annexes (e.g. Renewal, Line Extension, Variation II,

Variation IB) to implement the new statements, where applicable, in compliance with the revised Annex.

- For products with no regulatory activities MAHs should submit a type-IB variation (or an article 61(3) notification, where applicable) within 3 years after the publication of the revised guidance in the Annex.

ANNEX: EXCIPIENTS AND INFORMATION FOR THE PACKAGE LEAFLET

Explanatory Notes

The Annex to this guideline is available on the [EC website](#) and [EMA website](#). It is structured as follows:

Name

This is the name of the excipient using INN (or INN_M) accompanied by the salt if relevant, the Ph.Eur nomenclature where possible, the usual common name or failing this, the chemical name, together with the E number if available.

Updated on [date]

Where applicable, the date of the updated information is placed in this column and should be taken into account for the timeframe for implementation.

Route of Administration

This is necessary because the information may depend on the route of administration, e.g. for benzalkonium chloride the information relating to bronchospasm is particularly relevant for the inhalation route.

Threshold

The threshold is a value, equal to or above which it is necessary to provide the information stated; it is not a safety limit.

A threshold of 'zero' means that it is necessary to state the information in all cases where the excipient is present in the medicinal product.

Except where otherwise stated, thresholds are expressed as the quantity of excipient at the Maximum Daily Dose of the medicinal product as indicated in the SmPC.

When the text refers to the term 'per dose' it means the dose of the medicinal product.

It is accepted that excipients may only show an effect above a certain amount. This potential effect has been taken into account in the overall benefit/risk evaluation of the approved medicinal product.

Information for the Package Leaflet

The information is presented in a simple form, in clear and understandable terms for the patient.

The text applying to a specific population should be mentioned only if relevant.

If the pharmaceutical form is a solid form, e.g. tablet, capsule, suppository, powder in a sachet, it is recommended to express the amount per dosage unit (e.g. tablet, capsule etc.). If the pharmaceutical form is liquid, the amount per unit volume (e.g. milliliter etc.) is preferable.

Comments

Text in this column is not for the patient.

It is intended to give further information on the text in the preceding column, for the benefit of applicants and the competent authorities.

In some cases these comments may appear as a contraindication or as a warning to be included in the SmPC in an appropriate style and in the relevant section to ensure consistency with the package leaflet information.

For excipients reviewed from 2017, background scientific documents (Q&A and/or background report) can be found on the EMA website: www.ema.europa.eu > Human regulatory > Marketing authorisation > Product information > Reference and guidelines > [Excipients labelling](#)