CBG MEB

MEDICINES EVALUATION BOARD

Policy document

Guideline on the excipients in the label and the package leaflet of medicinal products for human use and MEB clarification of the Annex

MEB 8
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I. Introduction

This policy document contains the text of the European Commission's Guideline on the excipients in the labelling and package leaflet of medicinal products for human use.

The Guideline contains an Annex with a list of excipients which must be stated on the packaging and outlines which information regarding the excipients must be included in the package leaflet.

The Dutch translation of the Annex has been published at http://www.ema.europa.eu/docs/nl_NL/document_library/Scientific_guideline/2009/09/WC500003412.pdf

In chapter III of this policy document a clarification of the Annex by the MEB is included, in which the policy of the MEB regarding implementation and interpretation of the Annex is clarified.

II. Guideline on the 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:

- transdermal patch constituents
- excipient mixtures, e.g. those used for example in direct compression or in a film coat or polishfor 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 (INNM)) accompanied by the salt if relevant, or the European Pharmacopoeia name, their usual commonname 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 number 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.[1]

3. Proprietary flavours or fragrances may be declared in general terms (e.g. 'orange flavour', 'citrusfragrance/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 packageleaflet, 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 generaldescriptive term e.g. printing ink containing x, y, z. A general descriptive term may be used onthe labelling provided more information is given in the package leaflet. Any component with arecognised action or effect should be mentioned on the labelling.

8. Abbreviations for excipients should not be used. However, where justified for spaceconsiderations, abbreviations and/or latin names for excipients may appear on the labelling, on condition that the full name of the excipients in the national language appears in the SmPC and the package leaflet.

[1] 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

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.

III. MEB clarification of the Annex

The 'Guideline on Excipients in the labelling and package leaflet of medicinal products for human use' contains an Annex with a list of excipients which must be stated on the packaging and outlines which information regarding the excipients must be included in the package leaflet.

The Annex is structured as follows:

Name

This is the name of the excipient. Where possible, the INN or the European Pharmacopoeia nomenclature must be used, including the E number, if available.

Updated on [date]

If applicable, the date of the updated information is placed here. This date must be taken into consideration for the time line for implementation.

Route of administration

The route of administration is stated because the information may depend on it. For example, for benzalkonium chloride the information relating to bronchospasm is only relevant for the inhalation route.

Threshold

The threshold is a value, at which it is necessary to provide the stated information stated. It is not a safety limit which indicates how much excipient the product may contain.

It is generally accepted that excipients may only have an effect above a certain amount. This potential effect is taken into account in the evaluation of the product.

Unless stated otherwise, the thresholds are expressed as a maximum daily dosage of the **excipient in question**, taken as part of the medicinal product.

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.

Information for the package leaflet

This information should be stated in a simple form, in clear and patient-friendly wording.

The text frequently refers to the term 'per dosage', meaning the dosage of the medicinal product.

Given that dosages can be very variable, applicants must take into account the maximum single dosage of the medicinal product, as defined in paragraph 4.2 of the SmPC.

Hence the information sometimes contains, for example, the expression 'maximum x mg per dosage'.

If the pharmaceutical form is solid, for example a tablet, capsule, suppository, or powder in a sachet, it may be better to refer to the amount per tablet, capsule, etc. If the pharmaceutical form is liquid, it is preferable to state the amount per unit volume (e.g. millilitre, etc.).

Comments

The text in this column is not intended for the patient. This section provides additional information about the text in the previous column.

In some cases an SmPC text is included in the annex, but usually not. However, the information in the package leaflet must always correspond to the SmPC and must be in line with the information in the SmPC, as prescribed in Article 59, paragraph 1. Therefore, the information in both documents must be consistent.

Marketing authorisation holders must take this into account when implementing the information stated in the latest version of the Annex and, if applicable, submit a variation in order to update the SmPC and the package leaflet.

Please refer to the EMA website for background information about the modified excipients.