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

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

INTRODUCTION

This is a Commission guideline pursuant to Article 65 of Directive 2001/83/EC. It contains warning statements relating to the presence of certain excipients in medicinal products. Homeopathic medicinal products authorised through a special simplified registration procedure are not addressed in this guideline since for these homeopathic products there are specific labelling requirements according to Article 69.

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Article 54(c) requires that all excipients need to be declared on the labelling if the medicinal product is an injectable or a topical, or an eye preparation. Furthermore, Article 54 (1)(c) provides that: excipients known to have a recognised action or effect, and included in the guidelines published by the Commission pursuant to Article 65, need to be declared on the labelling of all other medicinal products.

Article 59 (1)(a) 2nd indent requires a full statement of the active substance and excipients 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(1)(c), 7th indent provides that the aforementioned information should include information on those excipients, knowledge of which is important for the safe and effective use of the medicinal product and included in the guidelines published by the Commission pursuant to Article 65.

Article 59(1) requires that the package leaflet must be in accordance with the SPC and shall be drawn up in accordance with the SPC. Therefore, consistent information should be stated in both documents.

PURPOSE

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

DEFINITIONS AND EXAMPLES

In general, excipients may be defined as the constituents of the pharmaceutical form that is taken by or administered to the patient, other than the active substance.

According to the Annex 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 – capsules, gelatine capsules, rectal capsules etc.

Further examples may include:

- 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.

NOMENCLATURE

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

1. Proprietary names should not be used for individual excipients. Excipients should be referred to by their recommended international nonproprietary name (INN), the European Pharmacopoeia name, or failing this, their usual common name.

2. The name of an excipient appearing in the Annex must 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 user package leaflet, in the section where the full qualitative composition is given.

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. Chemically modified excipients should be declared in such a way as to avoid confusion with the unmodified excipient (e.g. pre-gelatinised starch).

5. pH adjusters should be mentioned by name and their function may also be stated, e.g. hydrochloric acid for pH adjustment.

6. 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.

EXCIPIENTS IN THE LABELLING

According to Directive 2001/83/EC, all excipients in parenteral, ophthalmic and topical medicinal products must appear on the labelling. Topical medicinal products can be taken to include those medicinal products applied externally to the skin, respiratory products delivered to the lung by inhalation and any medicinal product delivered to the 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 the Commission's guideline, should be declared on the labelling. Such excipients are listed in Annex.

When a medicinal product contains any of these, the name of the excipient 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)(a) 2nd indent, of Directive 2001/83/EC, all of the 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 Article 59(1)(c) 4th and 7th indents of Directive 2001/83/EC, the fourth column in the Annex provides information corresponding to each excipient. The text of this information is in clear and understandable terms for the patient. However, taking into account that applicants may have different house styles for their package leaflets, it is not required that the information in the Annex should be applied verbatim to the package leaflet, so applicants may choose their own style to present this information to the patient, e.g. in a 'direct' or 'indirect' style. The content or meaning of the text must not be changed.

When a warning or information statement is required according to the Annex, it must be clear in the package leaflet and SPC 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. 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.

ANNEX: Excipients and Information for the Package Leaflet

Explanatory Notes

The Annex is structured as follows:

Name

This is the name of the excipient using INN or PhEur nomenclature where possible, including a reference to E-numbers where relevant

Route of administration

This is necessary because the information may depend upon the route of administration, e.g. for benzalkonium chloride the information relating to bronchospasm is relevant only for the respiratory route.

Threshold

It is accepted that excipients may only show an effect above a certain 'dose'.
Except where otherwise stated, thresholds are expressed as Maximum Daily Doses of the excipient in question, taken as part of a medicinal product.
The threshold is a value, equal to or above which it is necessary to provide the information stated.
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

The information is presented here in a simple form, in clear and understandable terms for the patient.
The text often refers to the term 'per dose' meaning dose of the medicinal product.
Since doses may be extremely variable, applicants must take into account
the maximum single dose of the medicinal product, as defined in the SPC, Section 4.2.
For this reason the information sometimes contains the expression
'up to x mg per dose', for example.

If the pharmaceutical form is a solid form, e.g. tablet, capsule, suppository, powder in a sachet, it may be better to refer to the amount per tablet, capsule etc.

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 in the SPC, worded in an appropriate style.