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

Guideline Title	**Excipients in the Label and Package Leaflet of Medicinal Products for Human Use**
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Date of first adoption	**June 1997**
Date of entry into force	**Applicable to all applications for a marketing authorisation and to all renewals made after September 1997**
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Previous titles/other references	**None**
Additional Notes	**This guideline outlines the nature of the information which should appear in the package leaflet, for those excipients which should be stated on the label. The annex provides a list of the excipients which should be stated on the label.**

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INTRODUCTION

LEGAL FRAMEWORK

Article 2.1 d) of Directive 92/27/EEC requires that all excipients need to be declared on the label if the product is an injectable, a topical or an eye preparation. Furthermore, Article 2.1 d) of Directive 92/27/EEC provides that: excipients known to have a recognised action or effect, and included in the guidelines published by the Commission pursuant to Article 12, need to be declared on the label of all other medicinal products.

Article 7.1c) states that the package leaflet must include a list of information which is necessary before taking the product. Article 7.1c), seventh 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 product and included in the guidelines published by the Commission pursuant to Article 12.

Although Article 12.2 of Directive 92/27/EEC provides that the guidelines should be adopted as a Commission Directive, it seems more appropriate, in the present case, and in accordance with the principle of subsidiarity, to adopt the present text in the form of a guideline as referred to in the Introduction to the Annex of Directive 75/318/EEC.

PURPOSE

This guideline is for use by applicants for a marketing authorisation. The Annex provides a list of the excipients which should be stated on the label.

Where appropriate, it outlines the nature of the information which should appear in the package leaflet, for the excipients which should be stated on the label. The precise text of this information needs to be formulated in consumer understandable language, but the meaning must remain in accordance with what is in this guideline.

One or more specimens or 'mock-ups' of the sales presentation and the package leaflet are required, by in Article 4§9 of Directive 65/65/EEC and Article 10§1 of Directive 92/27/EEC to accompany marketing authorisation applications. Applicants for a marketing authorisation should use this guideline when preparing these 'mock-ups'. A mock-up is a flat artwork design in full colour, presented so that, (following cutting and folding, where necessary), it provides a replica of both the outer and immediate packaging so that the three dimensional presentation of the label text is clear.

Samples of the finalised outer and immediate packaging and of the package leaflet must be submitted, to the competent authority, for approval, before commercialisation of the product.

EXCIPIENTS ON THE LABEL

For parenteral products, topical products and ophthalmic products all excipients must appear on the label. Topical products can be taken to include all inhaled medicines. For all other medicinal products, only those excipients known to have a recognised action or effect need to be declared on the label.

The excipients appearing in the Annex have a recognised action or effect: Therefore when a medicinal product contains any of these it must be stated on the label, together with a statement such as: 'see leaflet for further information'. The label statement of these excipients should be phrased so that it does not imply that these are the only excipients present in the product; therefore, 'includes…' would be preferable to 'contains…'.

However certain excipients in the Annex only need to be declared on the label in certain circumstances, related to the dose form and/or the quantity, as specified in the third column of the Annex.

EXCIPIENTS IN THE LEAFLET

1. According to Article 7.1a)-second indent, of Directive 92/27/EEC, all of the excipients must be stated on the package leaflet by name. Thus, even those excipients which are present in very small amounts should be stated in the leaflet, including:
   - the constituents of ingested capsule shells;
   - the constituents of a compound excipient preparation used; for example in direct compression or in a film coat or a polish for an ingested dose form;
   - the constituents of printing inks used to mark the ingested dose form;
   - pH adjusters in parenterals (these will also appear on the label);
   - diluents present, for example, in herbal extracts or vitamin concentrates;
   - the constituents in a mixture of chemically related components; (e.g. polyols or preservatives).
2. In line with the provisions of Article 7.1c) -fourth indent- of Directive 92/27/EEC, the fourth column in the Annex provides information corresponding to each excipient. The text of this information should to be put into 'consumer understandable' language

Nomenclature for excipients

1. The excipients appearing in the Annex are referred to by their international non-proprietary name (INN), as recommended by the World Health Organisation or, failing this, their usual common name.
2. The **E number** alone may be used for an excipient on the label, provided that the full name (INN where it exists, or usual common name), and the E number are stated in the user package leaflet in the section where the full qualitative composition is given.
3. Where the full composition of a **flavour or fragrance** is not known to the marketing authorisation holder, it should be declared in general terms (e.g. 'orange flavour', 'citrus fragrance/perfume'), and any of the components which are known should be stated (e.g. 'orange flavour including orange oil and maltodextrin').

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

ANNEX

Excipients for Label and corresponding Information for Leaflet

Name	**E number**	**Only required on the label when:-**	**Information in Leaflet** (*this should be put into consumer understandable language)*
Arachis oil		always and whenever arachis oil appears, peanut oil should appear beside it	
Aspartame	E 951	always	contains a source of phenylalanine
Benzalkonium chloride		always, for ophthalmic products only	Known to discolour soft contact lenses
Benzoic acid and Benzoates	E 210 to E 213	always	Benzoic acid is a mild irritant to the skin, eyes and mucous membrane. It may increase the risk of jaundice in newborn babies
Benzyl alcohol		always, for parenteral products only	contraindicated in infants or young children; up to 3 years old
Boric acid its salts and esters		always	contraindicated in infants or young children; up to 3 years old
Bovine aprotinin		always	
Bronopol		always	
Butylated hydroxyanisole	E 320	always	Irritant to the eyes, skin and mucous membranes.
Butylated hydroxytoluene	E 321	always	Irritant to the eyes, skin and mucous membranes.
Chlorobutanol		always	
Dimethyl sulfoxide		always	Can cause stomach upset, diarrhoea, drowsiness and headache.

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Excipients for Label and corresponding Information for Leaflet

Name	**E number**	**Only required on the label when:**	**Information in Leaflet** (*this should be put into consumer understandable language)*
Ethanol		The % in the product should be stated on the label If a single dose of the product contains more than 0.05g ethanol; "see leaflet" should be on the label	If the quantity in the maximum daily dose is between 0.05 and 3g: WARNING: This product contains ... vol % of ethanol. Each dose contains up to ... g of alcohol. Harmful for those suffering from liver disease, alcoholism, epilepsy, brain injury or disease as well as for pregnant women and children. May modify or increase the effect of other medicines. If the quantity in the maximum daily dose exceeds 3g:- • WARNING: This product contains ... vol % of ethanol. Each dose contains up to ... g of ethanol. Caution! This medicine must not been taken by children, pregnant women and people suffering from liver disease, epilepsy and alcoholism' and 'brain injury or disease. Reactions in road traffic and while operating machinery may be lowered. May modify or increase the effect of other medicines. • Topical products:- Frequent applications to the skin produces irritation and dry skin.
Formaldehyde		the content of the unbound substance in the finished product exceeds 0.05% w/w	If present in products taken internally it can cause stomach upset and diarrhoea. The vapour from it can irritate eyes and nose. If present in topical products: 'known to cause allergy'
Fructose		always	This medicinal product contains ...g of fructose. When taken according to the dosage recommendations, each dose supplies up to ...g of fructose. Unsuitable in hereditary fructose intolerance Due to the possibility of not yet detected congenital fructose intolerance, this medicinal product should be only given to babies and infants after consultation with a physician.
Galactose		always	This medicinal product contains ...g of galactose. When taken according to the dosage recommendations each dose supplies up to ...g of glucose. Unsuitable for people with lactase insufficiency, galactosaemia or glucose/galactose malabsorption syndrome.

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Excipients for Label and corresponding Information for Leaflet

Name	**E number**	**Only required on the label when:**	**Information in Leaflet** (*this should be put into consumer understandable language)*
Glucose		always	This medicinal product contains ...g of glucose. When taken according to the dosage recommendations each dose supplies up to ...g of glucose.
Glycerol		always, in oral dose forms	Harmful in high doses. Can cause headache and can cause stomach upset and diarrhoea.
Invert sugar		the quantity in the maximum daily dose exceeds 5g	This medicinal product contains ...g of glucose and ...g of fructose. When taken according to the dosage recommendations each dose supplies up to ...g of glucose and ...g of fructose. Unsuitable for people with hereditary fructose intolerance.
Lactose		the quantity in the maximum daily dose exceeds 5g	This medicinal product contains ...g of lactose. When taken according to the dosage recommendations each dose supplies up to ...g of lactose. Unsuitable for people with lactase insufficiency, galactosaemia or glucose/galactose malabsorption syndrome.
Lanolin		always	
Mannitol		always	
Organic mercury compounds		always	can cause kidney damage
Paraformaldehyde		the content of the unbound substance in the medicinal product exceeds 0.5% w/w	If present in products taken internally: Can cause stomach upset and diarrhoea. The vapour is irritant to the eyes, and nose. If present in topical products: 'known to cause allergy'
Parahydroxybenzoates and their esters	E 214 to E219	the content of the unbound substance in the medicinal product exceeds 0.5%w/w	Known to cause urticaria. Generally delayed type reactions, such as contact dermatitis. Rarely immediate reaction with urticaria and bronchospasm.
Phenylalanine		always	Harmful for people with phenylketonuria
Phenylmercuric salts (acetate, borate, nitrate)		always	Irritant to the skin. Topical application to eyes has been associated with mercurialentis and atypical band keratopathy

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Excipients for Label and corresponding Information for Leaflet

Name	**E number**	**Only required on the label when:**	**Information in Leaflet** (*this should be put into consumer understandable language)*
Polyethoxylated castor oils		always	Warning for parenterals only:- hypersensitivity -drop in blood pressure, inadequate circulation, dyspnoea, hot flushes Warning for oral dose forms: nausea, vomiting, colic, severe purgation (high doses) – Not to be given when intestinal obstruction is present.
Polyols		the content in the medicinal product exceeds 10%	may cause diarrhoea
Potassium		always	Harmful to people on a low potassium diet. Hyperkalaemia – can cause stomach upset and diarrhoea following oral administration. For products administrated I.V.: can cause pain at the site of injection or phlebitis
Propylene glycol its salts and esters		always	
Salicylic acid		always	mild irritant - can cause dermatitis
Sodium		the quantity in the maximum daily dose exceeds 200mg sodium	may be harmful to people on a low sodium diet
Sorbic acid and its salts	E200 to E203	always	Irritant: can cause dermatitis
Sorbitol		the quantity in the maximum daily dose exceeds 2g	This medicinal product contains ...g of sorbitol. When taken according to the dosage recommendations each dose supplies up to ...g of sorbitol. Unsuitable in hereditary fructose intolerance. Can cause stomach upset and diarrhoea .
Soya oil		always	

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Excipients for Label and corresponding Information for Leaflet

Name	**E number**	**Only required on the label when:**	**Information in Leaflet** (*this should be put into consumer understandable language)*
Sucrose (Saccharose)		the quantity in the maximum daily dose exceeds 5g	This medicinal product contains ...g of sucrose. When taken according to the dosage recommendations each dose supplies up to ...g of sucrose. Unsuitable in hereditary fructose intolerance, glucose-galactose malabsorption syndrome, or sucrase-isomaltase deficiency.
Sulphites (metabisulphites)	E 220 to E 228	always	Can cause allergic-type reactions including anaphylactic symptoms and bronchospasm in susceptible people, especially those with a history of asthma or allergy.
Tartrazine and other azo colouring agents	E 102 E 110 E 122 to E 124 E 151	always	Can cause allergic-type reactions including asthma. Allergy is more common in those people who are allergic to aspirin.
Urea		always	For products given I.V.:- may cause venous thrombosis or phlebitis. Topical applications may be irritant to sensitive skin.
Wheat starch		always	may be harmful to people with coeliac disease