MINISTRY OF PUBLIC HEALTH

ORDER
for approval of Guideline on excipients which must be specified in the label and package leaflet of medicinal products for human use

Taking into account:

- provisions of Law No. 95/2006 on healthcare reform, Title XVII - The medicinal product, especially Article 775 e), Article 763 d), Article 769 (1) c) and f) and Article 769 (2) c);

- Government Ordinance No. 125/1998 related to the set up, organisation and functioning of the National Medicines Agency, approved as amended through Law No. 594/2002, as amended,

based on Government Decision No. 862/2006 on organisation and functioning of the Ministry of Public Health,

on seeing the Approval Report of the Pharmaceutical Directorate No. E.N. 4.710/2006,

the Minister of public health hereby issues the following order:

Article 1. - The Guideline on excipients which must be specified on the label and package leaflet of medicinal products for human use is approved in accordance with the Annex, which is integral part of the present order.

Article 2. - On this order coming into force, any other contrary dispositions shall be repealed.

Article 3. - The present order shall be published in the Official Gazette of Romania, Part I.

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The present order is a translation into Romanian and an adaptation of the European Commission Guideline "Excipients in the label and package leaflet of medicinal products for human use" of July 2003.

Minister of public health,
Gheorghe Eugen Nicolăescu

Bucharest, 2 October 2006
No. 1202.

ANNEX

GUIDELINE
on excipients which must be specified in the label and package leaflet of medicinal products for human use

CHAPTER I
Scope

Article 1. – (1) The present Guideline is for use by the National Medicines Agency *(NMA),* for Marketing Authorisation Applicants and Marketing Authorisation Holders.

(2) The Annex, which is integral part of the present Guideline, provides a list of the excipients which should be stated on the package and outlines the information which should appear in the package leaflet, for these excipients; Provisions of the present Guideline do not apply to these substances when they are used as active substances.

Article 2. Homeopathic medicinal products authorised for a particular simplified procedure are not subject of the present Guideline, since there are specific requirements for these medicinal products concerning labelling, based on Article 779, Title XVII - The medicinal product of Law No. 95/2006 on healthcare reform.

CHAPTER II
Definitions and Excipient Categories

Article 3. - In general, excipients may be defined as constituents of the pharmaceutical form that is taken by or administered to the patient, other than the active substance.

Article 4. - According to Order of the Minister of public health No. 906/2006 on approval of Norms, Analytical, pharmacotoxicological and clinical norms and protocols in respect of the testing of medicinal products, such constituents may include:

a) colouring matter, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, flavouring and aromatic substances, etc.;

b) constituents intended to be ingested or otherwise administered to the patient, of the outer covering of medicinal products – capsules, gelatine capsules, rectal capsules, coated tablets, film-coated tablets etc.

Article 5. – Further Excipient Categories may include:

a) excipient mixtures, e.g. those used in direct compression or in a film coat or polish for an ingested dose form;

b) pH adjusters;

c) the constituents of printing inks used to mark the ingested dose form;

d) diluents present, for example, in herbal extracts or vitamin concentrates;

e) the constituents present in a mixture of chemically related components (e.g. preservatives).

Article 6. - In the context of this Guideline, definition from Article 3 does not include residues of substances arising from the manufacturing process, impurities, residual solvents, degradation products etc.

Article 7. – (1) 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.

(2) 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 in the Annex.

CHAPTER III
Nomenclature

Article 8. - The following apply to the names of all excipients on the label, package leaflet and in the Summary of Product Characteristics *(SPC)*.

a) Proprietary names should not be used for individual excipients; excipients should be referred to by their recommended international non-proprietary name (INN), the European Pharmacopoeia name or, failing this, their usual common name.

b) The name of an excipient appearing in the Annex must be accompanied by the E number if it exists. The E number alone (not accompanied by the excipient's name) may be used for an excipient on the package, provided that the full name and the E number are stated in the package leaflet, in the section where the full qualitative composition is given;

c) Proprietary flavours or fragrances may be declared in general terms (e.g. "orange flavour", "citrus fragrance"); any known major components or those with a recognised action or effect should be declared specifically;

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

e) pH adjusters should be mentioned by name and their function, e.g. hydrochloric acid for pH adjustment;

f) All components of compound excipients or mixtures should be declared, listed under a general descriptive term, e.g. printing ink containing x, y, z; the general descriptive term may be used on the label provided more information is given in the package leaflet. Any component with a recognised action or effect should be mentioned on the label and package leaflet.

CHAPTER IV
Excipients in the labelling

Article 9. - According to provisions of Article 763 (d) of Law No. 95/2006, all excipients in parenteral, ophthalmic and topical medicinal products must appear on the

label. Topical medicinal products may include those medicinal products applied externally on 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.

Article 10. - 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 label; such excipients are listed in the Annex.

Article 11. - When a medicinal product contains any of these excipients, the name of the excipient must be stated on the label, together with a statement such as "see leaflet for further information".

CHAPTER V
Excipients in the package leaflet

Article 12. - All of the excipients must be stated on the package leaflet from the quality point of view, according to the nomenclature defined in this Guideline.

Article 13. – (1) In line with the provisions of Article 769(1) (c) 4th and Article 769 (2) (c) of Law No. 95/2006, the fourth column in the Annex provides information corresponding to each excipient.

(2) The text of this information must be clear and in understandable terms for the patient.

Article 14. - 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 easily understand whether the warning relates to the excipient or the active substance.

Article 15. - (1) 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. "Ability to drive and operate machinery", "Pregnancy and Lactation", "Possible undesirable effects"; to simplify the presentation of the package leaflet, this information should appear only once.

(2) 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 alcohol (ethanol), it will be necessary to refer back to the excipient warnings section on "Ability to drive", "Pregnancy and Lactation", "Information for children" etc.

Annex to Guideline

Excipients and Information for the Package Leaflet

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Benzoic acid and benzoates, such as: benzoic acid (E210) sodium benzoate (E211) potassium benzoate (E212)	Topical	Zero	Mildly irritant to the skin, eyes and mucous membranes.	
	Parenteral	Zero	May increase the risk of jaundice in new-born babies.	
Sorbic acid and salts	Topical	Zero	May cause adverse local cutaneous skin reactions, (e.g. contact dermatitis).	
Azo colouring agents, such as : Tartrazine (E102), Orange yellow S, Sunset yellow FCT (Orange yellow S, Sunset yellow FCF (E110), Azorubine, Carmoisine (Azorubine, Carmoisine) (E122), Amarant (Amaranth) (E123), Cochineal red A, Ponceau 4R red (Cochineal Red A) (E124), Brilliant Black BN, Black PN (Brilliant Black BN, Black PN) (E151)	Oral	Zero	May cause allergic reactions	

Benzyl alcohol	Parenteral	Exposures less than 90mg/kg/day 90mg/kg/day	Must not be given to premature babies or neonates. May cause toxic reactions and allergic reactions in infants and children up to 3 years old. Must not be given to premature babies or neonates. Due to the risk of fatal toxic reactions arising from exposure to benzyl alcohol in excess of 90 mg/kg/day, this product should not be used in premature babies or neonates.	SPC: "allergic" should be expressed as "anaphylactoid" The amount of benzyl alcohol in mg per <volume> should be stated in the package leaflet and SPC. The amount of benzyl alcohol in mg per <volume> should be stated in the package leaflet and SPC.
Cetostearyl alcohol including Cetyl alcohol	Topical	Zero	May cause adverse local cutaneous skin reactions, (e.g. contact dermatitis).	
Stearyl alcohol	Topical	Zero	May cause adverse local cutaneous skin reactions, (e.g. contact dermatitis).	
Wheat starch	Oral	Zero	Suitable for people with coeliac disease. Patients with wheat allergy (different from celiac disease) should not take this medicine.	Wheat starch may contain gluten, but only in trace amounts, and is therefore considered safe for people with coeliac disease. (Gluten in wheat starch is limited by the test for total protein described in the European Pharmacopoeia monograph.)
Aprotinin	Topical	Zero	May cause hypersensitivity or severe allergic reactions.	The topical route in this case refers to sites that may have access to the circulation (e.g. wounds, body cavities etc.)
Aspartam (E951)	Oral	Zero	Contains a source of phenylalanine. May be harmful for people with phenylketonuria	
Balsam of Peru	Topical	Zero	May cause cutaneous adverse reactions.	

Bronopol	Topical	Zero	May cause local skin reactions (e.g. contact dermatitis).	
Butylated hydroxyanisole (E320)	Topical	Zero	May cause local cutaneous skin reactions (e.g. Contact dermatitis), or irritation to the eyes and mucous membranes.	
Butylated Hydroxytoluene (E321)	Topical	Zero	May cause local cutaneous skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.	
Chlorocresol	Topical Parenteral	Zero	May cause allergic reactions	
Benzalkonium chloride	Ocular	Zero	May cause eye irritation. Avoid contact with soft contact lenses. Remove contact lenses prior to application and wait at least 15 minutes before reinsertion. Known to discolour soft contact lenses.	
	Topical		Irritant, may cause skin reactions.	
	Respiratory	10µg/ delivered dose	May cause bronchospasm.	
Organic Mercury compounds, such as: Thiomersal, Phenylmercuric nitrate, acetate, borate)	Ocular	Zero	May cause allergic reactions.	See EMEA Public Statement, 8 July 1999, Ref. EMEA/20962/99
	Topical	Zero	May cause local cutaneous skin reactions (e.g. contact dermatitis) and color modifications.	
	Parenteral	Zero	This medicinal product contains (thiomersal) as a preservative and it is possible that you/your child may experience an allergic reaction after administration. Tell your doctor if you/your child have/has any known allergies.	See EMEA Public Statement, 8 July 1999, Ref. EMEA/20962/99

			Tell your doctor if you/your child experience(s) any health problems after administration of a vaccine.	Additional statement to be mentioned for vaccines
Dimethyl sulphoxide	Topical	Zero	May be irritant to the skin.	
Alcohol (Ethanol)	Oral and Parenteral	Less than 100mg/ dose	This medicinal product contains small amounts of ethanol (alcohol), less than 100mg/dose.	This statement is to provide reassurance to parents and children concerning the low levels of alcohol in the product.
		100mg–3g/dose	This medicinal product contains ... vol % alcohol (ethanol), i.e. up to ... mg/dose, equivalent to ... ml beer, ... ml wine/dose. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease, or epilepsy.	The package leaflet should give the equivalent volume of beer and wine, nominally calculated assuming 5 % vol and 12% vol ethanol respectively. Separate warning statements may be needed in different parts of the PL.
	Oral and Parenteral	3g/dose	This medicinal product contains ... vol % ethanol (alcohol), i.e. up to ... mg/dose, equivalent to ... ml beer, ... ml wine/dose. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease or epilepsy. The amount of alcohol in this medicinal product may alter the effects of other medicines. The amount of alcohol in this medicinal product may impair your ability to drive or use machines.	

Phenylalanine	All	Zero	This medicinal product contains phenylalanine. May be harmful for people with phenylketonuria.	
Formaldehyde	Topical	Zero	May cause adverse local skin reactions (e.g. contact dermatitis).	
	Oral	Zero	May cause stomach upset and diarrhoea	
Fructose	Oral Parenteral	Zero	If you have been told by your doctor that you have an intolerance to certain sugars, contact your doctor before taking/using this medicinal product	SPC proposal: Patients with rare hereditary problems of fructose intolerance should not take this medicinal product**.**
		5g	Contains x g fructose/dose. This should be taken into account in patients with diabetes mellitus.	
	Oral liquids, lozenges and chewable tablets	Zero	May be harmful to the teeth.	Information to be included only when the medicinal product may be intended for chronic use, e.g. for two weeks or more.
Galactose	Parenteral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.	SPC proposal: Patients with rare hereditary problems of galactose intolerance e.g. galactosaemia should not take this medicinal product.
	Oral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.	SPC proposal: Patients with rare hereditary problems of galactose intolerance e.g. galacotosaemia, or glucose galactose malabsorption should not take this medicinal product.
	Oral Parenteral	5g	Contains x g glucose/dose. This should be taken into account in patients with diabetes mellitus.	
Glycerol	Oral	10g/dose	May cause headache, stomach upset and diarrhoea.	

	Rectal	1g	May have a mild laxative effect.	
Glucose	Oral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.	SPC proposal: Patients with rare glucose-galactose malabsorption should not take this medicinal product
	Oral Parenteral	5g	Contains x g galactose/dose. This should be taken into account in patients with diabetes mellitus.	
	Oral liquids, lozenges and chewable tablets	Zero	May be harmful to the teeth.	Information to be included only when the medicinal product may be intended for chronic use, e.g. for two weeks or more.
Heparin (as an excipient)	Parenteral	Zero	May cause allergic reactions and reduced blood cell counts which may affect the blood clotting system. Patients with a history of heparin-induced allergic reactions should avoid the use of heparin-containing medicinal products.	
Lactitol (E966)	Oral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.	SPC proposal: Patients with rare hereditary problems of fructose intolerance, galactose intolerance, galactosaemia or glucose-galactose malabsorption should not take this medicine.
		10g	May have a mild laxative effect. Calorific value 2.1 kcal/g lactitol.	
Lactose	Oral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.	SPC proposal: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

		5g	Contains X g lactose (X/2g glucose and X/2g galactose)/dose. This should be taken into account in patients with diabetes mellitus	
Lanolin	Topical	Zero	May cause local skin reactions (e.g. contact dermatitis)	
Latex Natural rubber (latex)	All	Zero	The container of this medicinal product contains latex rubber. May cause severe allergic reactions.	Not a typical excipient, but a warning is considered necessary
Maltitol (E965) and Isomaltitol (E953), Maltitol Liquid (see Hydrogenated Glucose Syrup)	Oral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.	SPC proposal: Patients with rare hereditary problems of fructose intolerance should not take this medicinal product.
		10g	May have a mild laxative effect. Calorific value 2.3 kcal/g maltitol (or isomaltitol).	
Mannitol (E421)	Oral	10g	May have a mild laxative effect.	
Parahydroxybenzoates and their esters, for example: Ethyl hydroxybenzoate (E214), Propylhydroxybenzoate (E216), Sodium propylhydroxybenzoate (E217), Methylhydroxybenzoate (E218), Sodium methylhydroxybenzoate (E219)	Oral Ocular Topical	Zero	May cause allergic reactions (possibly delayed).	
	Parenteral Respiratory	Zero	May cause allergic reactions (possibly delayed) and, exceptionally, bronchospasm.	

Potassium	Parenteral	Less than 1mmol/dose	This medicinal product contains potassium, less than 1mmol (39mg)/dose, i.e. essentially "potassium-free".	Information relates to a threshold based on the total amount of K+ in the medicinal product. It is especially relevant to products used in paediatric doses, to provide information to prescribers and reassurance to parents concerning the low level of K+ in the medicinal product.
	Parenteral Oral	1mmol/dose	This medicinal product contains Xmmol (or Ymg) potassium/dose. To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.	
	Parenteral-intravenous	30mmol/l	May cause pain at the site of injection.	
Propylene glycol and its esters	Topical	Zero	May cause cutaneous irritation	
	Oral Parenteral	400mg/kg adults 200mg/kg children	May cause alcohol-like symptoms	
Hydrogenated Glucose Syrup (or Maltitol liquid)	Oral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.	SPC proposal: Patients with rare hereditary problems of fructose intolerance should not take this medicinal product.
		10g	May have a mild laxative effect. Calorific value 2.3 kcal/g of hydrogenated glucose syrup.	

Sodium	Parenteral	under 1mmol/dose	This medicinal product contains less than 1mmol sodium (23mg)/dose, i.e. essentially "sodium- free".	Information relates to a threshold based on the total amount of Na^+ in the medicinal product. It is especially relevant to products used in paediatric doses, to provide information to prescribers and reassurance to parents concerning the low level of Na+ in the product.
	Oral Parenteral	1mmol/dose	This medicinal product contains x mmol (or y mg) sodium per <dose>. To be taken into consideration by patients on a controlled sodium diet.	
Sorbitol (E420)	Oral Parenteral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.	SPC proposal: Patients with rare hereditary problems of fructose intolerance should not take this medicinal product.
	Oral	10g	May have a mild laxative effect. Calorific value 2.6kcal/g sorbitol.	
Sulphites including metabisulphites For example: Sulphur dioxide (E220), Sodium sulphite (E221), Sodium bisulphate (E222), Sodium metabisulphite (E223), Potassium metabisulphite (E224), Potassium bisulphite (E228).	Oral Parenteral Respiratory	Zero	May rarely cause severe hypersensitivity reactions and Bronchospasm.	
Arachis oil (peanut oil)	All	Zero	(Medicinal product) contains arachis oil (peanut oil). If you are allergic to peanut or soy, do not use this medicinal product.	Purified arachis oil may contain peanut protein. The European Pharmacopoeia monograph does not contain a test for residual protein. SPC: contraindication.

Bergamot oil Bergapten	Topical	Zero	May increase sensitivity to UV light (natural and artificial sunlight).	Does not apply when Bergapten is shown to be absent from the oil.
Castor oil polyoxyl and hydrogenated castor oil polyoxyl	Parenteral	Zero	May cause severe allergic reactions.	
	Oral	Zero	May cause stomach upset and diarrhoea.	
	Topical	Zero	May cause adverse skin reactions.	
Soy oil and Hydrogenated Soy oil	All	Zero	(Medicinal product) contains soya oil. If you are allergic to peanut or soya, do not use this medicinal product.	In line with Arachis oil. SPC: contraindication.
Sesame oil	All	Zero	May rarely cause severe allergic reactions.	
Xylitol	Oral	10g	May have a laxative effect. Calorific value 2.4 kcal/g xylitol.	
Sugar	Oral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.	SPC proposal: Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or saccharose-isomaltose deficiency should not take this medicinal product**.**
		5g	Contains Xg sugar/dose. This should be taken into account in patients with diabetes mellitus.	
	Oral liquids, lozenges and chewable tablets	Zero	May be harmful to the teeth.	Information to be included only when the medicinal product may be intended for chronic use, e.g. for two weeks or more.
Invert sugar	Oral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.	SPC proposal: Patients with rare hereditary problems of fructose intolerance or glucose-galactose malabsorption should not take this medicinal product**.**

		5g	Contains Xg fructose and galactose mixture/dose. This should be taken into account in patients with diabetes mellitus.	
	Oral liquids, lozenges and chewable tablets	Zero	May be harmful to the teeth.	Information to be included only when the medicinal product may be intended for chronic use, e.g. for two weeks or more.

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Explanatory Notes on the structure to the Annex to the present Guideline on Excipients and Information for the Package Leaflet

"Name"

In this column is written the name of the excipient using INN or European Pharmacopoeia nomenclature where possible, including a reference to E-numbers where relevant.

"Route of administration"

This column 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 easily 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. tablets, capsule, suppository, powder in a sachet, it may be better to refer to the amount per tablets, capsule etc.

"Comments"

The text in this column is not intended for the patient.

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

In some cases these comments may appear as a contraindication in the SPC, worded in an appropriate style.