9 October 2017
EMA/CHMP/302620/2017 corr. 1*

Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' (SANTE-2017-11668)

Excipients and information for the package leaflet

Agreed by CHMP Excipients Drafting Group	6 July 2017
Adopted by EMA Committee for Medicinal Products for Human Use (CHMP)	20 July 2017
Endorsed by European Commission's Notice to Applicants Group	4 October 2017
Date of publication	9 October 2017

This document updates and replaces the Annex previously included in the Guideline CPMP/463/00 Rev. 1.

It is an integral part of the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' (SANTE-2017-11668).

Keywords	***Excipient, Package Leaflet, Labelling***

* See pages 23-25 for details.

Excipients and information for the package leaflet

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
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.).
Arachis oil (peanut oil)		All	Zero	<Medicinal product> contains arachis oil (peanut oil). If you are allergic to peanut or soya, do not use this medicinal product.	Purified arachis oil may contain peanut protein. The PhEur monograph does not contain a test for residual protein. SmPC: contraindication.
Aspartame (E 951)	**09/10/2017**	Oral	Zero	This medicine contains x mg aspartame in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>>. Aspartame is a source of phenylalanine. It may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.	Aspartame is hydrolysed in the gastrointestinal tract when orally ingested. One of the major hydrolysis products is phenylalanine. Information to consider for the SmPC: Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age.
Azo colouring agents e.g.: Tartrazine (E 102) Sunset yellow FCF (E 110) Azorubine, carmoisine (E 122) Amaranth (E 123) Ponceau 4R, cochineal Red A (E 124) Brilliant black BN, black PN (E 151)		Oral	Zero	May cause allergic reactions.	
Balsam of Peru		Topical	Zero	May cause skin reactions.	
Benzalkonium chloride	**09/10/2017**	All	Zero	This medicine contains x mg benzalkonium chloride in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>>.	

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Benzalkonium chloride	09/10/2017	Ocular	Zero	Benzalkonium chloride may be absorbed by soft contact lenses and may change the colour of the contact lenses. You should remove contact lenses before using this medicine and put them back 15 minutes afterwards. Benzalkonium chloride may also cause eye irritation, especially if you have dry eyes or disorders of the cornea (the clear layer at the front of the eye). If you feel abnormal eye sensation, stinging or pain in the eye after using this medicine, talk to your doctor.	From the limited data available, there is no difference in the adverse event profile in children compared to adults. Generally, however, eyes in children show a stronger reaction for a given stimulus than the adult eye. Irritation may have an effect on treatment adherence in children. Benzalkonium chloride has been reported to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. Should be used with caution in dry eye patients and in patients where the cornea may be compromised. Patients should be monitored in case of prolonged use.
Benzalkonium chloride	09/10/2017	Nasal	Zero	Benzalkonium chloride may cause irritation or swelling inside the nose, especially if used for a long time.	Long-term use may cause oedema of the nasal mucosa.
Benzalkonium chloride	09/10/2017	Inhalation	Zero	Benzalkonium chloride may cause wheezing and breathing difficulties (bronchospasm), especially if you have asthma.	
Benzalkonium chloride	09/10/2017	Cutaneous	Zero	Benzalkonium chloride may irritate the skin. You should not apply this medicine to the breasts if you are breast-feeding because the baby may take it in with your milk.	Use during pregnancy and lactation is not expected to be associated with harmful effects to the mother as cutaneous absorption of benzalkonium chloride is minimal. Not for application to mucosa.
Benzalkonium chloride	09/10/2017	Oromucosal, rectal and vaginal	Zero	Benzalkonium chloride may cause local irritation.	
Benzoic acid (E 210) and benzoates e.g.: Sodium benzoate (E 211) Potassium benzoate (E 212)	09/10/2017	All	Zero	This medicine contains x mg <benzoic acid/benzoate salt> in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>>.	

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Benzoic acid (E 210) and benzoates e.g.: Sodium benzoate (E 211) Potassium benzoate (E 212)	09/10/2017	Oral, parenteral	Zero	<Benzoic acid/Benzoate salt> may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).	Increase in bilirubinaemia following its displacement from albumin may increase neonatal jaundice which may develop into kernicterus (non-conjugated bilirubin deposits in the brain tissue).
Benzoic acid (E 210) and benzoates e.g.: Sodium benzoate (E 211) Potassium benzoate (E 212)	09/10/2017	Topical	Zero	<Benzoic acid/Benzoate salt> may cause local irritation.	May cause non-immunologic immediate contact reactions by a possible cholinergic mechanism.
Benzoic acid (E 210) and benzoates e.g.: Sodium benzoate (E 211) Potassium benzoate (E 212)	09/10/2017	Topical	Zero	<Benzoic acid/Benzoate salt> may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).	Absorption through the immature skin of neonates is significant.
Benzyl alcohol	09/10/2017	All	Zero	This medicine contains x mg benzyl alcohol in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>>. Benzyl alcohol may cause allergic reactions.	
Benzyl alcohol	09/10/2017	Oral, parenteral	Zero	Benzyl alcohol has been linked with the risk of severe side effects including breathing problems (called “gasping syndrome”) in young children. Do not give to your newborn baby (up to 4 weeks old), unless recommended by your doctor.	Intravenous administration of benzyl alcohol has been associated with serious adverse events and death in neonates (“gasping syndrome”). The minimum amount of benzyl alcohol at which toxicity may occur is not known. Warning in section 4.4 in the SmPC should be given if used in neonates.
Benzyl alcohol	09/10/2017	Oral, parenteral	Zero	Do not use for more than a week in young children (less than 3 years old), unless advised by your doctor or pharmacist.	Increased risk due to accumulation in young children.
Benzyl alcohol	09/10/2017	Oral, parenteral	Zero	Ask your doctor or pharmacist for advice if you are pregnant or breast-feeding. This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called “metabolic acidosis”).	

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Benzyl alcohol	**09/10/2017**	Oral, parenteral	Zero	Ask your doctor or pharmacist for advice if you have a liver or kidney disease. This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called “metabolic acidosis”).	High volumes should be used with caution and only if necessary, especially in subjects with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis).
Benzyl alcohol	**09/10/2017**	Topical	Zero	Benzyl alcohol may cause mild local irritation.	
Bergamot oil (containing 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.
Boric acid (and borates)	**09/10/2017**	All	1 mg B/day*	Do not give to a child less than 2 years old as this medicine contains boron and may impair fertility in the future.	* 1 mg B (Boron) = 5.7 mg boric acid. See Q&A document (EMA/CHMP/619104/2013) for further calculations. Amount of boron per age group which may impair fertility if exceeded: **Age** **Safety limit** < 2 years 1 mg B/day < 12 years 3 mg B/day < 18 years** 7 mg B/day ≥ 18 years** 10 mg B/day ** This amount may also cause harm to the unborn child.

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Boric acid (and borates)	**09/10/2017**	All	3 mg B/day*	Do not give to a child less than 12 years old as this medicine contains boron and may impair fertility in the future.	* 1 mg B (Boron) = 5.7 mg boric acid. See Q&A document (EMA/CHMP/619104/2013) for further calculations. Amount of boron per age group which may impair fertility if exceeded: **Age** **Safety limit** < 2 years 1 mg B/day < 12 years 3 mg B/day < 18 years** 7 mg B/day ≥ 18 years** 10 mg B/day ** This amount may also cause harm to the unborn child.
Boric acid (and borates)	**09/10/2017**	All	7 mg B/day*	Do not give to a child less than 18 years old as this medicine contains boron and may impair fertility in the future. If you are pregnant, talk to your doctor before taking this medicine as it contains boron which may be harmful to your baby.	* 1 mg B (Boron) = 5.7 mg boric acid. See Q&A document (EMA/CHMP/619104/2013) for further calculations. Amount of boron per age group which may impair fertility if exceeded: **Age** **Safety limit** < 2 years 1 mg B/day < 12 years 3 mg B/day < 18 years** 7 mg B/day ≥ 18 years** 10 mg B/day ** This amount may also cause harm to the unborn child.
Bronopol		Topical	Zero	May cause local skin reactions (e.g. contact dermatitis).	
Butylated hydroxyanisole (E 320)		Topical	Zero	May cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.	

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Butylated hydroxytoluene (E 321)		Topical	Zero	May cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.	
Cetostearyl alcohol including Cetyl alcohol		Topical	Zero	May cause local skin reactions (e.g. contact dermatitis).	
Chlorocresol		Topical, parenteral	Zero	May cause allergic reactions.	
Cyclodextrins e.g.: Alfadex Betadex (E 459) γ-cyclodextrin Sulfobutyl-ether-β-cyclodextrin (SBE-β-CD) Hydroxypropyl betadex Randomly methylated β-cyclodextrin (RM-β-CD)	**09/10/2017**	All	20 mg/kg/day	This medicine contains x mg cyclodextrin(s) in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>>. Do not use in children less than 2 years old unless recommended by your doctor.	Cyclodextrins (CDs) are excipients which can influence the properties (such as toxicity or skin penetration) of the active substance and other medicines. Safety aspects of CDs have been considered during the development and safety assessment of the drug product, and are clearly stated in the SmPC. There is insufficient information on the effects of CDs in children < 2 years old. Therefore, a case by case judgement should be made regarding the risk/benefit for the patient. Based on animal studies and human experience, harmful effects of CDs are not to be expected at doses below 20 mg/kg/day.
Cyclodextrins e.g.: Alfadex Betadex (E 459) γ-cyclodextrin Sulfobutyl-ether-β-cyclodextrin (SBE-β-CD) Hydroxypropyl betadex Randomly methylated β-cyclodextrin (RM-β-CD)	**09/10/2017**	Oral	200 mg/kg/day	Cyclodextrins may cause digestive problems such as diarrhoea.	At high doses cyclodextrins can cause reversible diarrhoea and cecal enlargement in animals.

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Cyclodextrins e.g.: Alfadex Betadex (E 459) γ-cyclodextrin Sulfobutyl-ether-β-cyclodextrin (SBE-β-CD) Hydroxypropyl betadex Randomly methylated β-cyclodextrin (RM-β-CD)	09/10/2017	Parenteral	200 mg/kg/day and use for > 2 weeks	If you have a kidney disease, talk to your doctor before you receive this medicine.	In children less than 2 years, the lower glomerular function may protect against renal toxicity, but can lead to higher blood levels of cyclodextrins. In patients with moderate to severe renal dysfunction accumulation of cyclodextrins may occur.
Dimethyl sulphoxide		Topical	Zero	May be irritant to the skin.	
Ethanol		Oral, parenteral	Less than 100 mg per dose	This medicinal product contains small amounts of ethanol (alcohol), less than 100 mg per <dose>.	This statement is to provide reassurance to parents and children concerning the low levels of alcohol in the product.
Ethanol		Oral, parenteral	100 mg per dose	This medicinal product contains ... vol % ethanol (alcohol), i.e. up to ... mg per <dose>, equivalent to ... ml beer, ... ml wine per <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.
Ethanol		Oral, parenteral	3 g per dose	This medicinal product contains ... vol % ethanol (alcohol), i.e. up to ... mg per <dose>, equivalent to ... ml beer, ... ml wine per <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.	

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Formaldehyde		Topical	Zero	May cause local skin reactions (e.g. contact dermatitis).	
Formaldehyde		Oral	Zero	May cause stomach upset and diarrhea.	
Fragrances containing allergens* **(See appendix)**	**09/10/2017**	Topical	Zero	This medicine contains fragrance with <allergen(s)>*. <Allergen(s)>* may cause allergic reactions.	*< >: fragrance allergens listed in appendix. In addition to allergic reactions in sensitised patients, non-sensitised patients may become sensitised. Benzyl alcohol is listed as one of the 26 fragrance allergens but can also be used as an excipient. When benzyl alcohol is used as an excipient (in addition to a fragrance or not), the label of this excipient applies.
Fructose	**09/10/2017**	Oral, parenteral	Zero	This medicine contains x mg fructose in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>>.	The additive effect of concomitantly administered products containing fructose (or sorbitol) and dietary intake of fructose (or sorbitol) should be taken into account.
Fructose	**09/10/2017**	Oral	Zero	*[If the medicine is in contact with teeth (e.g. oral liquids, lozenges or chewable tablets) and is intended for long term use:]* Fructose may damage teeth.	Oral products used frequently or over a long period of time, e.g. for two weeks or longer.
Fructose	**09/10/2017**	Intravenous (IV)	Zero	If you (or your child) have hereditary fructose intolerance (HFI), a rare genetic disorder, you (or your child) must not receive this medicine. Patients with HFI cannot break down fructose in this medicine, which may cause serious side effects. You must tell your doctor before receiving this medicine if you (or your child) have HFI or if your child can no longer take sweet foods or drinks because they feel sick, vomit or get unpleasant effects such as bloating, stomach cramps or diarrhoea.	Patients with hereditary fructose intolerance (HFI) must not be given this medicine unless strictly necessary. Babies and young children (below 2 years of age) may not yet be diagnosed with hereditary fructose intolerance (HFI). Medicines (containing fructose) given intravenously may be life-threatening and must be contraindicated in this population unless there is an overwhelming clinical need and no alternatives are available. A detailed history with regard to HFI symptoms has to be taken of each patient prior to being given this medicinal product.

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Fructose	09/10/2017	Oral, parenteral (other than IV)	5 mg/kg/day	If your doctor has told you that you (or your child) have an intolerance to some sugars or if you have been diagnosed with hereditary fructose intolerance (HFI), a rare genetic disorder in which a person cannot break down fructose, talk to your doctor before you (or your child) take or receive this medicine.	Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.
Galactose		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.	SmPC proposal: Patients with rare hereditary problems of galactose intolerance e.g. galactosaemia<, or glucose-galactose malabsorption> should not take this medicine.
Galactose		Oral, parenteral	5 g	Contains x g galactose per dose. This should be taken into account in patients with diabetes mellitus.	
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.	SmPC proposal: Patients with rare glucose-galactose malabsorption should not take this medicine.
Glucose		Oral, parenteral	5 g	Contains x g glucose per dose. This should be taken into account in patients with diabetes mellitus.	
Glucose		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.
Glycerol (E 422)		Oral	10 g per dose	May cause headache, stomach upset and diarrhea.	
Glycerol (E 422)		Rectal	1 g	May have a mild laxative effect.	
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 medicines.	
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.	SmPC proposal: Patients with rare hereditary problems of fructose intolerance or glucose-galactose malabsorption should not take this medicine.

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Invert sugar		Oral	5 g	Contains x g of a mixture of fructose and glucose per dose. This should be taken into account in patients with diabetes mellitus.	
Invert sugar		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.
Lactitol (E 966)		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.	SmPC proposal: Patients with rare hereditary problems of fructose intolerance, galactose intolerance, galactosaemia or glucose-galactose malabsorption should not take this medicine.
Lactitol (E 966)		Oral	10 g	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.	SmPC proposal: Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Lactose		Oral	5 g	Contains x g lactose (x/2 g glucose and x/2 g galactose) per dose. This should be taken into account in patients with diabetes mellitus.	
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.
Macrogolglycerol ricinoleate (castor oil polyoxyl) **Macrogolglycerol hydroxystearate** (castor oil polyoxyl hydrogenated)		Parenteral	Zero	May cause severe allergic reactions.	
Macrogolglycerol ricinoleate (castor oil polyoxyl) **Macrogolglycerol hydroxystearate** (castor oil polyoxyl hydrogenated)		Oral	Zero	May cause stomach upset and diarrhea.	

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Macrogolglycerol ricinoleate (castor oil polyoxyl) **Macrogolglycerol hydroxystearate** (castor oil polyoxyl hydrogenated)		Topical	Zero	May cause skin reactions.	
Maltitol (E 965) **Isomalt (E 953)** (isomaltitol) **Maltitol liquid** (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.	SmPC proposal: Patients with rare hereditary problems of fructose intolerance should not take this medicine.
Maltitol (E 965) **Isomalt (E 953)** (isomaltitol) **Maltitol liquid** (hydrogenated glucose syrup)		Oral	10 g	May have a mild laxative effect. Calorific value 2.3 kcal/g <maltitol><isomalt>.	
Mannitol (E 421)		Oral	10 g	May have a mild laxative effect.	
Organic mercury compounds e.g.: Thiomersal Phenylmercuric nitrate/acetate/borate		Ocular	Zero	May cause allergic reactions.	See EMEA Public Statement, 8 July 1999, Ref. EMEA/20962/99
Organic mercury compounds e.g.: Thiomersal Phenylmercuric nitrate/acetate/borate		Topical	Zero	May cause local skin reactions (e.g. contact dermatitis) and discolouration.	

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Organic mercury compounds e.g.: Thiomersal Phenylmercuric nitrate/acetate/borate		Parenteral	Zero	This medicinal product contains (thiomersal) as a preservative and it is possible that <you/your child> may experience an allergic reaction. Tell your doctor if <you/your child> have/has any known allergies.	See EMEA Public Statement, 8 July 1999, Ref. EMEA/20962/99
Organic mercury compounds e.g.: Thiomersal Phenylmercuric nitrate/acetate/borate		Parenteral	Zero	Tell your doctor if you/your child have/has experienced any health problems after previous administration of a vaccine.	Additional statement to be mentioned for vaccines.
Parahydroxybenzoates and their esters e.g.: Ethyl p-hydroxybenzoate (E 214) Sodium ethyl p-hydroxybenzoate (E 215) Propyl p-hydroxybenzoate Sodium propyl p-hydroxybenzoate Methyl p-hydroxybenzoate (E 218) Sodium methyl p-hydroxybenzoate (E 219)		Oral Ocular Topical	Zero	May cause allergic reactions (possibly delayed).	

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Parahydroxybenzoates and their esters e.g.: Ethyl p-hydroxybenzoate (E 214) Sodium ethyl p-hydroxybenzoate (E 215) Propyl p-hydroxybenzoate Sodium propyl p-hydroxybenzoate Methyl p-hydroxybenzoate (E 218) Sodium methyl p-hydroxybenzoate (E 219)		Parenteral Inhalation	Zero	May cause allergic reactions (possibly delayed), and exceptionally, bronchospasm.	
Phenylalanine	**09/10/2017** *Corrigendum 19/11/2018*	All	Zero	This medicine contains x mg phenylalanine in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>>. Phenylalanine may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.	
Phosphate buffers	**09/10/2017**	Ocular	Zero	This medicine contains x mg phosphates in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>>. If you suffer from severe damage to the clear layer at the front of the eye (the cornea), phosphates may cause in very rare cases cloudy patches on the cornea due to calcium build-up during treatment.	Corresponding SmPC statement in Section 4.8 (Undesirable effects): “Cases of corneal calcification have been reported very rarely in association with the use of phosphate containing eye drops in some patients with significantly damaged corneas.”
Potassium		Parenteral	Less than 1 mmol per dose	This medicine contains potassium, less than 1 mmol (39 mg) per <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 product.

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Potassium		Oral, parenteral	1 mmol per dose	This medicine contains x mmol (or y mg) potassium per <dose>. To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.	
Potassium		Intravenous (IV)	30 mmol/l	May cause pain at the site of injection.	
Propylene glycol (E 1520) and esters of propylene glycol	**09/10/2017**	All	1 mg/kg/day	This medicine contains x mg propylene glycol in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>>.	
Propylene glycol (E 1520) and esters of propylene glycol	**09/10/2017**	Oral, parenteral	1 mg/kg/day	If your baby is less than 4 weeks old, talk to your doctor or pharmacist before giving them this medicine, in particular if the baby is given other medicines that contain propylene glycol or alcohol.	Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce serious adverse effects in neonates.
Propylene glycol (E 1520) and esters of propylene glycol	**09/10/2017**	Oral, parenteral	50 mg/kg/day	If your child is less than 5 years old, talk to your doctor or pharmacist before giving them this medicine, in particular if they use other medicines that contain propylene glycol or alcohol.	Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce adverse effects in children less than 5 years old.
Propylene glycol (E 1520) and esters of propylene glycol	**09/10/2017**	Oral, parenteral	50 mg/kg/day	If you are pregnant or breast-feeding, do not take this medicine unless recommended by your doctor. Your doctor may carry out extra checks while you are taking this medicine.	While propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, it may reach the foetus and was found in milk. As a consequence, administration of propylene glycol to pregnant or lactating patients should be considered on a case by case basis.
Propylene glycol (E 1520) and esters of propylene glycol	**09/10/2017**	Oral, parenteral	50 mg/kg/day	If you suffer from a liver or kidney disease, do not take this medicine unless recommended by your doctor. Your doctor may carry out extra checks while you are taking this medicine.	Medical monitoring is required in patients with impaired renal or hepatic functions because various adverse events attributed to propylene glycol have been reported such as renal dysfunction (acute tubular necrosis), acute renal failure and liver dysfunction.

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Propylene glycol (E 1520) and esters of propylene glycol	**09/10/2017**	Oral, parenteral	500 mg/kg/day	Propylene glycol in this medicine can have the same effects as drinking alcohol and increase the likelihood of side effects. Do not use this medicine in children less than 5 years old. Use this medicine only if recommended by a doctor. Your doctor may carry out extra checks while you are taking this medicine.	Various adverse events, such as hyperosmolality, lactic acidosis; renal dysfunction (acute tubular necrosis), acute renal failure; cardiotoxicity (arrhythmia, hypotension); central nervous system disorders (depression, coma, seizures); respiratory depression, dyspnoea; liver dysfunction; haemolytic reaction (intravascular haemolysis) and haemoglobinuria; or multisystem organ dysfunction, have been reported with high doses or prolonged use of propylene glycol. Therefore doses higher than 500 mg/kg/day may be administered in children > 5 years old but will have to be considered case by case. Adverse events usually reverse following weaning off of propylene glycol, and in more severe cases following hemodialysis. Medical monitoring is required.
Propylene glycol (E 1520) and esters of propylene glycol	**09/10/2017**	Cutaneous	50 mg/kg/day	Propylene glycol may cause skin irritation. Do not use this medicine in babies less than 4 weeks old with open wounds or large areas of broken or damaged skin (such as burns) without talking to your doctor or pharmacist.	
Propylene glycol (E 1520) and esters of propylene glycol	**09/10/2017**	Cutaneous	500 mg/kg/day	Propylene glycol may cause skin irritation. Because this medicine contains propylene glycol, do not use it on open wounds or large areas of broken or damaged skin (such as burns) without checking with your doctor or pharmacist.	
Sesame oil		All	Zero	May rarely cause severe allergic reactions.	

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Sodium	**09/10/2017**	Oral, parenteral	Less than 1 mmol (23 mg) per dose	This medicine contains less than 1 mmol sodium (23 mg) per <dosage unit><unit volume>, that is to say essentially 'sodium-free'.	1 mmol of sodium (Na) = 23 mg Na = 58.4 mg salt (NaCl). Information relates to a threshold based on the total amount of sodium in the medicinal product. It is especially relevant to products used in children or in patients on a low sodium diet, to provide information to prescribers and reassurance to parents or patients concerning the low level of sodium in the product.
Sodium	**09/10/2017**	Oral, parenteral	1 mmol (23 mg) per dose	This medicine contains x mg sodium (main component of cooking/table salt) in each <dosage unit><unit volume>. This is equivalent to y% of the recommended maximum daily dietary intake of sodium for an adult.	For parenterals with variable (e.g. weight-based) dosing sodium content may be expressed in mg per vial. Proposed wording for SmPC: "This medicinal product contains x mg sodium per <dosage unit>, equivalent to y% of the WHO recommended maximum daily intake of 2 g sodium for an adult."

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Sodium	**09/10/2017**	Oral, parenteral	17 mmol (391 mg) in the maximum daily dose	Talk to your doctor or pharmacist if you need <Z> or more <dosage units> daily for a prolonged period, especially if you have been advised to follow a low salt (sodium) diet.	This applies only to products for which the labelled posology allows the product to be taken on a daily basis for > 1 month or repeated use for more than 2 days every week. 17 mmol (391 mg) is approximately 20% of the WHO adult recommended maximum daily dietary intake of 2 g sodium and is considered to represent 'high' sodium. This is also relevant for children, where the maximum daily intake is considered to be proportional to adults and based on energy requirements. <Z doses> reflects the lowest number of dosage units for which the threshold of 17 mmol (391 mg) of sodium is reached/ exceeded. Round down to the nearest whole number. For SmPC wording please refer to PRAC recommendation: "*1.3. Sodium-containing effervescent, dispersible and soluble medicines – Cardiovascular events*" (EMA/PRAC/234960/2015).
Sodium laurilsulfate	**09/10/2017** *Corrigendum 19/11/2018*	Cutaneous	Zero	This medicine contains x mg sodium laurilsulfate in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>>. Sodium laurilsulfate may cause local skin reactions (such as stinging or burning sensation) or increase skin reactions caused by other products when applied on the same area.	The thickness of the skin varies considerably according to the body site and with age and can be an important factor in the sensitivity to sodium laurilsulfate (SLS). Sensitivity to SLS will also vary according the type of formulation (and effects of other excipients), the concentration of SLS, contact time and patient population (children, hydration level, skin color and disease). Patient populations with decreased skin barrier functions such as in atopic dermatitis are more sensitive to the irritant properties of SLS.
Sorbic acid (E 200) and salts		Topical	Zero	May cause local skin reactions, (e.g. contact dermatitis).	

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Sorbitol (E 420)	**09/10/2017**	Oral, parenteral	Zero	This medicine contains x mg sorbitol in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>>.	The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account. The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.
Sorbitol (E 420)	**09/10/2017**	Intravenous (IV)	Zero	Sorbitol is a source of fructose. If you (or your child) have hereditary fructose intolerance (HFI), a rare genetic disorder, you (or your child) must not receive this medicine. Patients with HFI cannot break down fructose, which may cause serious side effects. You must tell your doctor before receiving this medicine if you (or your child) have HFI or if your child can no longer take sweet foods or drinks because they feel sick, vomit or get unpleasant effects such as bloating, stomach cramps or diarrhoea.	Patients with hereditary fructose intolerance (HFI) must not be given this medicine unless strictly necessary. Babies and young children (below 2 years of age) may not yet be diagnosed with hereditary fructose intolerance (HFI). Medicines (containing sorbitol/fructose) given intravenously may be life-threatening and should be contraindicated in this population unless there is an overwhelming clinical need and no alternatives are available. A detailed history with regard to HFI symptoms has to be taken of each patient prior to being given this medicinal product.
Sorbitol (E 420)	**09/10/2017**	Oral, parenteral (other than IV)	5 mg/kg/day	Sorbitol is a source of fructose. If your doctor has told you that you (or your child) have an intolerance to some sugars or if you have been diagnosed with hereditary fructose intolerance (HFI), a rare genetic disorder in which a person cannot break down fructose, talk to your doctor before you (or your child) take or receive this medicine.	Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.
Sorbitol (E 420)	**09/10/2017**	Oral	140 mg/kg/day	Sorbitol may cause gastrointestinal discomfort and mild laxative effect.	
Soya oil **Hydrogenated soya 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. SmPC: contraindication.
Stearyl alcohol		Topical	Zero	May cause local skin reactions (e.g. contact dermatitis).	

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Sucrose		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.	SmPC proposal: Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
Sucrose		Oral	5 g	Contains x g of sucrose per dose. This should be taken into account in patients with diabetes mellitus.	
Sucrose		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.
Sulphites including metabisulphites e.g.: Sulphur dioxide (E 220) Sodium sulphite (E 221) Sodium bisulphite (E 222) Sodium metabisulphite (E 223) Potassium metabisulphite (E 224) Potassium bisulphite (E 228)		Oral Parenteral Inhalation	Zero	May rarely cause severe hypersensitivity reactions and bronchospasm.	
Wheat starch (containing gluten)	**09/10/2017** *Corrigendum 19/11/2018*	Oral	Zero	This medicine contains only very low levels of gluten (from wheat starch)<. It is regarded as 'gluten-free'*> and is very unlikely to cause problems if you have coeliac disease. One <dosage unit> contains no more than x micrograms of gluten. If you have wheat allergy (different from coeliac disease) you should not take this medicine. *[* The statement 'gluten-free' applies only if the gluten content in the medicinal product is less than 20 ppm.]*	The name of the excipient on the packaging should be: 'Wheat starch'.
Wool fat (lanolin)		Topical	Zero	May cause local skin reactions (e.g. contact dermatitis).	

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Xylitol (E 967)		Oral	10 g	May have a laxative effect. Calorific value 2.4 kcal/g xylitol.	

Appendix: European Union list of fragrance allergens requiring labelling on cosmetic and detergent products

Substance	CAS No
3-Methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-3-buten-2-one	127-51-5
Amyl cinnamal	122-40-7
Amylcinnamyl alcohol	101-85-9
Anisyl alcohol	105-13-5
Benzyl alcohol	100-51-6
Benzyl benzoate	120-51-4
Benzyl cinnamate	103-41-3
Benzyl salicylate	118-58-1
Cinnamal	104-55-2
Cinnamyl alcohol	104-54-1
Citral	5392-40-5
Citronellol	106-22-9
Coumarin	91-64-5
d-Limonene	5989-27-5
Eugenol	97-53-0
Farnesol	4602-84-0
Geraniol	106-24-1
Hexyl cinnamaldehyde	101-86-0
Hydroxycitronellal	107-75-5
Hydroxymethylpentyl-cyclohexenecarboxaldehyde	31906-04-4
Isoeugenol	97-54-1
Lilial	80-54-6
Linalool	78-70-6
Methyl heptine carbonate	111-12-6
Oak moss	90028-68-5
Tree moss	90028-67-4

Corrigendum 1 (19/11/2018)

Phenylalanine, column “Route of Administration”

Rationale: correction of an editorial mistake.

Previous version:

Phenylalanine	Oral

Corrected version:

Phenylalanine	All

Sodium laurilsulfate, column “Name”

Rationale: E number deleted for consistency with the Annex III of Regulation (EC) No 1333/2008 on food additives.

Previous version:

Sodium laurilsulfate (E 487)

Corrected version:

Sodium laurilsulfate

Wheat starch (containing gluten), columns “Information for the Package Leaflet” and “Comments”

Changes and rationale:

Column “Information for the Package Leaflet”: The wording is clarified and consistent with the food regulation (EU) No 828/2014. The statement "gluten-free" relates to the gluten content in the finished medicinal product and not in wheat starch.

Column “Comments”: The first paragraph has been deleted. According to EDQM, there is no correlation between the total protein content and the gluten content. Therefore calculation should be based directly on the batch information about its gluten content.

Previous version:

Wheat starch (containing gluten)	Wheat starch in this medicine contains only very low levels of gluten <regarded as gluten-free*> and is very unlikely to cause problems if you have coeliac disease. One <dosage unit> contains no more than x micrograms of gluten. If you have wheat allergy (different from coeliac disease) you should not take this medicine. *[* The statement “regarded as gluten-free” applies only if the gluten content in wheat starch is less than 20 ppm.]*	In compliance with the Ph. Eur. monograph, the protein limit of 0.3% in wheat starch (total protein test), means that there is no more than 100 ppm (µg/g) of gluten present in the wheat starch. The maximum level of gluten in the excipient can be calculated based on this information (protein content). The name of the excipient on the packaging should be: “Wheat starch”.

Corrected version:

Wheat starch (containing gluten)	This medicine contains only very low levels of gluten (from wheat starch)<. It is regarded as ‘gluten-free’*> and is very unlikely to cause problems if you have coeliac disease. One <dosage unit> contains no more than x micrograms of gluten. If you have wheat allergy (different from coeliac disease) you should not take this medicine. *[* The statement* ’gluten-free’ *applies only if the gluten content in the medicinal product is less than 20 ppm.]*	The name of the excipient on the packaging should be: ’Wheat starch’.

In practice,

- For products < 20 ppm the PIL should state:

"This medicine contains only very low levels of gluten (from wheat starch). It is regarded as 'gluten-free' and is very unlikely to cause problems if you have coeliac disease…."

- For products > 20 ppm the PIL should state:

"This medicine contains only very low levels of gluten (from wheat starch) and is very unlikely to cause problems if you have coeliac disease…"