15 January 2026
MCA-GL-134, version1 - 2026
MCA Technical Working Group

Guideline for Excipients in the Labelling and Patient Information Leaflet of Medicines for Human Use

Draft written by MCA Technical Working Group	12 December 2025
Release for and start of public consultation	15 December 2025
End of consultation (deadline for comments)	07 January 2026
Agreed by <Working group(s)/Departments>	13 January 2026
Approved by MCA Executive Director	15 January 2026
Date of coming into effect	19 January 2026

This is a new guideline.

Comments should be provided by using the template (MCA-F-021/03) for Submission of Comments and sent to info@mca.gm

Keywords	excipient, package leaflet, patient information leaflet, PIL, summary of products characteristics, SmPC, labelling

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Guideline for Excipients in the Labelling and Patient Information Leaflet of Medicines for Human Use

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Executive summary

This guideline has been developed by using the adoption approach based on the work-plan agreed in March 2023 by the Joint Technical Working Group for Guidelines in Marketing Authorization (TWG-MAG). The TWG-MAG consists of two representatives each of the national medicines regulatory authorities (NMRA) of Liberia (LMHRA, Liberia Medicines and Health Products Regulatory Authority), Sierra Leone (PBSL, Pharmacy Board of Sierra Leone), The Gambia (MCA, Medicines Control Agency), and Ghana (FDA, Food and Drugs Authority) and is facilitated by the GHPP PharmTrain2 Project team of the Federal Institute for Drugs and Medical Devices (BfArM, Germany).

Version 1 of the Guideline on Excipients for the National Medicines Regulatory Authorities of Ghana, Liberia, Sierra Leone, and The Gambia was finalised on 04 June 2024 for annotation in the MCA guideline.

This document should be read in conjunction with relevant sections of the MCA *Guideline for Marketing Authorisation (Registration) of Medicines* and other applicable guidance.

Information on the parent guideline

Guideline

Title: Excipients in the labelling and package leaflet of medicinal products for human use

Author(s): European Commission, Health and Food Safety Directorate-General

Document No: Brussels, March 2018 SANTE-2017-11668

Version No: (Not applicable)

Date of issue: March 2018

Source (e.g. website link):
https://www.gmp-compliance.org/files/guidemgr/guidelines_excipients_march2018_en.pdf
(Accessed April 2025)
Revision 2, NOTICE TO APPLICANTS, VOLUME 2C, Guidelines

Medicinal products for human use
Safety, environment and information

Annex:

Title: Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'
Excipients and information for the package leaflet

Author(s):

Document No: EMA/CHMP/302620/2017 Rev. 1*

Version No: (Not applicable)

Date of issue: 22 November 2019

Source (e.g. website link):
https://www.ema.europa.eu/en/documents/scientific-guideline/annex-european-commission-guideline-excipients-labelling-and-package-leaflet-medicinal-products-human-use-sante-2017-11668-revision-1_en.pdf
(Accessed April 2025)

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	22 November 2019

This document 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***

1 General aspects and terms deviating from parent guideline

1.1. For the purpose of consistency with other MCA guidelines, the terms of the parent guideline (left column) shall read as synonymous to the following terms (right column):

Parent guideline term	**Synonymous term**
Medicinal Product	Medicine
Package leaflet	Patient information leaflet

2 Text of Parent Guideline with MCA's annotations

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

INTRODUCTION

In accordance with Article 65(e) of Directive 2001/83/EC[1] 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.

[1] DIRECTIVE 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67).

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 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 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 common name 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[2] 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.
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. 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 package leaflet, 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 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.
8. Abbreviations for excipients should not be used. However, where justified for space considerations, 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.

[2] 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

For new marketing authorisation applications, implementation of the information as per the latest revision of the guideline Annex should be followed.

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.

MCA's Annotation: The sentences "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.

Are amended as follows:

"Marketing authorisation holders (MAHs) are encouraged to use the first upcoming regulatory procedure affecting Product Information Annexes (e.g. Renewal, Line Extension, Major Variation, Minor Variation) to implement the new statements, where applicable, in compliance with the revised Annex.

For products with no regulatory activities MAHs should submit a minor variation (or notification, where applicable) within 3 years after the publication of the revised guidance in the Annex.

Rationale: In The Gambia the variation II corresponds to the reporting type of major variation and the variation IB to the reporting type of minor variation.

ANNEX: EXCIPIENTS AND INFORMATION FOR THE PACKAGE LEAFLET

Explanatory Notes

The Annex to this guideline is available on the EC website and EMA website. It is structured as follows:

Name

This is the name of the excipient using INN (or INNM) accompanied by the salt if relevant, the Ph.Eur nomenclature where possible, the usual common name or failing this, the chemical name, together with the E number if available.

Updated on [date]

Where applicable, the date of the updated information is placed in this column and should be taken into account for the timeframe for implementation.

Route of Administration

This is necessary because the information may depend on the route of administration, e.g. for benzalkonium chloride the information relating to bronchospasm is particularly relevant for the inhalation route.

Threshold

The threshold is a value, equal to or above which it is necessary to provide the information stated; it is not a safety limit.
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.
Except where otherwise stated, thresholds are expressed as the quantity of excipient at the Maximum Daily Dose of the medicinal product as indicated in the SmPC.
When the text refers to the term 'per dose' it means the dose of the medicinal product.
It is accepted that excipients may only show an effect above a certain amount. This potential effect has been taken into account in the overall benefit/risk evaluation of the approved medicinal product.

Information for the Package Leaflet

The information is presented in a simple form, in clear and understandable terms for the patient. The text applying to a specific population should be mentioned only if relevant.
If the pharmaceutical form is a solid form, e.g. tablet, capsule, suppository, powder in a sachet, it is recommended to express the amount per dosage unit (e.g. tablet, capsule etc.). If the pharmaceutical form is liquid, the amount per unit volume (e.g. milliliter etc.) is preferable.

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 or as a warning to be included in the SmPC in an appropriate style and in the relevant section to ensure consistency with the package leaflet information.

For excipients reviewed from 2017, background scientific documents (Q&A and/or background report) can be found on the EMA website: www.ema.europa.eu > Human regulatory > Marketing authorisation > Product information > Reference and guidelines > Excipients labelling

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.

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 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").	
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.
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.	See comments above.

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
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.	See comments above.
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.	
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.

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**	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.
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	**22/11/2019**	Oral Parenteral Inhalation	Zero	This medicine contains x mg of alcohol (ethanol) in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>><(y% w/<w><v>)>. The amount in <dose><volume> of this medicine is equivalent to less than A ml beer or B ml wine. The small amount of alcohol in this medicine will not have any noticeable effects.	Where ethanol is present as a processing agent (for example in tablet coating) or extraction solvent and is evaporated off (under the level of ICH Q3C) there is no need to mention ethanol in patient information. To calculate the equivalent volume of beer and wine, assume the ethanol content of beer to be 5% v/v (alcohol by volume, ABV), which is equivalent to 4% w/v, and of wine to be 12.5% v/v or 10% w/v (the specific gravity of ethanol has been approximated as 0.8). Volumes of beer and wine (A and B) should be rounded up to the next whole number.

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Ethanol	**22/11/2019**	Oral Parenteral Inhalation	15 mg/kg per dose	This medicine contains x mg of alcohol (ethanol) in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>><(y% w/<w><v>)>. The amount in <dose><volume> of this medicine is equivalent to A ml beer or B ml wine. The amount of alcohol in this medicine is not likely to have an effect in adults and adolescents, and its effects in children are not likely to be noticeable. It may have some effects in younger children, for example feeling sleepy. The alcohol in this medicine may alter the effects of other medicines. Talk to your doctor or pharmacist if you are taking other medicines. If you are pregnant or breast-feeding, talk to your doctor or pharmacist before taking this medicine. If you are addicted to alcohol, talk to your doctor or pharmacist before taking this medicine.	To calculate the equivalent volume of beer and wine, assume the ethanol content of beer to be 5% v/v (alcohol by volume, ABV), which is equivalent to 4% w/v, and of wine to be 12.5% v/v or 10% w/v (the specific gravity of ethanol has been approximated as 0.8). Where relevant, the interactions of ethanol should be stated in the SmPC (section 4.5). Suggestion for information in the SmPC: A dose of (select maximum dose) of this medicine administered to (a child A years of age and weighing B kg or an adult weighing 70 kg) would result in exposure to C mg/kg of ethanol which may cause a rise in blood alcohol concentration (BAC) of about D mg/100 ml (see Appendix 1 of report EMA/CHMP/43486/2018). For comparison, for an adult drinking a glass of wine or 500 ml of beer, the BAC is likely to be about 50 mg/100 ml. Co-administration with medicines containing e.g. propylene glycol or ethanol may lead to accumulation of ethanol and induce adverse effects, in particular in young children with low or immature metabolic capacity. When a dose is given over prolonged period (e.g. by slow infusion over several hours), the rise in BAC will be less and the effects of ethanol may be reduced. In such cases the package leaflet and SmPC should include a statement such as: Because this medicine is usually given slowly over XX hours, the effects of alcohol may be reduced.

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Ethanol	**22/11/2019**	Oral Parenteral Inhalation	75 mg/kg per dose	This medicine contains x mg of alcohol (ethanol) in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>> (y% w/<w><v>). The amount in <dose><volume> of this medicine is equivalent to A ml beer or B ml wine. The alcohol in this preparation is likely to affect children. These effects may include feeling sleepy and changes in behaviour. It may also affect their ability to concentrate and take part in physical activities. The amount of alcohol in this medicine can affect your ability to drive or use machines. This is because it may affect your judgement and how fast you react. If you have epilepsy or liver problems, talk to your doctor or pharmacist before taking this medicine. The amount of alcohol in this medicine may alter the effects of other medicines. Talk to your doctor or pharmacist if you are taking other medicines. If you are pregnant or breast-feeding, talk to your doctor or pharmacist before taking this medicine. If you are addicted to alcohol, talk to your doctor or pharmacist before taking this medicine.	See comments above.

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Ethanol	**22/11/2019**	Cutaneous	Zero	This medicine contains x mg alcohol (ethanol) in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>> (y% w/<w><v>). It may cause burning sensation on damaged skin.	In neonates (pre-term and term newborn infants), high concentrations of ethanol may cause severe local reactions and systemic toxicity due to significant absorption through immature skin (especially under occlusion). The corresponding warning in the SmPC/PL should be added if appropriate. Depending on the product and concentration of ethanol, the warning "flammable" may be necessary. Inclusion of warnings on use near an open flame, lit cigarette or some devices (e.g. hairdryers) should be considered.
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.

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
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.
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.

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
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.
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.	

MCA's Annotation:

1. Lactose wording concerning serious (congenital) genetic disorders (*Threshold zero*)

'Patients with congenital lactase deficiency, galactosaemia or glucose-galactose intolerance must not be given this medicine unless absolutely necessary'.

2. Lactose wording concerning lactose intolerance

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
(*Where lactose ≤ 400 mg per dose*): 'The small amount of lactose in each dose is unlikely to cause symptoms of lactose intolerance'. If the wording for genetic disorders above is also included, add 'in other patients' (*Where lactose > 400 mg per dose*): 'The small amount of lactose in each dose may cause symptoms of intolerance If the wording for genetic disorders above is also included, add 'in other patients' 3. Lactose wording concerning cow's milk protein allergy (*Threshold zero; only applicable to lactose of bovine origin*) for products given orally: 'Patients who are allergic to cow's milk proteins must not be given this medicine unless absolutely necessary' for products given parentally: 'Patients who are allergic to cow's milk must not be given this medicine as it may contain trace amounts of cow's milk protein' 4. Lactose wording concerning diabetes (*Threshold 5 g per dose*) 'Lactose is a source of glucose. Patients with concurrent diabetes should take account of the amount of lactose in this medicine (x in each <dosage unit>)' **Rationale:** For the product information published as part 3 and 4 in the WHO Public Assessment Reports for products prequalified via the full assessment route some exceptions apply which MCA adapted.					
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.	
Macrogolglycerol ricinoleate (castor oil polyoxyl) **Macrogolglycerol hydroxystearate** (castor oil polyoxyl hydrogenated)		Topical	Zero	May cause skin reactions.	

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
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.	
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

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	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.
Para hydroxybenzoates 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).	
Para hydroxybenzoates 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.	

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
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.
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.

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	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.
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.

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**	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.	
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).

MCA's Annotation:

Section 2 QUALITATIVE AND QUANTITATIVE COMPOSITION of SmPC: "*Excipients with potential clinical effect"*

This heading is not included for sodium if the medicine is 'essentially sodium free'; instead a statement is included in section Heading and warning only if product contains 1mmol (23 mg) sodium or more

Section 6. PHARMACEUTICAL PARTICULARS of SmPC: 6.1 "*List of excipients***"**

If a product contains an API(s) and/or excipients that are sodium salts, but the total quantity of sodium is less than 1 mmol (23 mg) per dosage unit: This medicine is essentially 'sodium-free'. It contains less than 1 mmol sodium (23 mg) per dosage unit.

If the medicine is 'essentially sodium free', i.e. contains excipients with sodium but the total quantity of sodium is less than 1 mmol (23 mg) per dosage unit, a statement in section 6.1 is included:

'This medicine is essentially 'sodium-free'. It contains less than 1 mmol sodium (23 mg) per <dosage unit, e.g. tablet>'

Rationale: For the product information published as part 3 and 4 in the WHO Public Assessment Reports for products prequalified via the full assessment route some exceptions apply which MCA adapted

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
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).	
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.

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
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).	
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.

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Sulphites including meta-bisulphites 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).	
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

3 Annotations to aspects not included in parent guideline

MCA's Annotation: The legal basis should be included as follows: This guideline has to be read in conjunction with the Medicines and Related Product Act, 2014. This guideline is coherent with national/regional frameworks and policies. The usage of this guideline by MCA is supported/embedded in the Act.

Rationale: Legal basis has to be followed by MCA therefore reference is made.

References used for this guideline adoption approach

- Medicines and Related Products Act, 2014
- MCA Guideline for Marketing Authorisation (Registration) of Medicines
- MCA Guideline for Pharmaceutical Development (MCA-GL-131)
- MCA Guideline for Impurities in New Active Pharmaceutical Ingredients (MCA-GL-126)
- MCA Guideline for Impurities in New Finished Pharmaceutical Products (MCA-GL-127)
- MCA Guideline for Specifications: Test Procedures and Acceptance Criteria for new Active Pharmaceutical Ingredients and new Finished Pharmaceutical Products (MCA-GL-125)
- MCA Guideline for Stability Testing of Active Pharmaceutical Ingredients and Finished Pharmaceutical Products (MCA-GL-123)
- WHO/PQT: medicines, Note on Reference Guideline for Excipients with a known action or effect, Guidance Document 28 October 2025 https://extranet.who.int/prequal/sites/default/files/document_files/20250318_2-Note%20PQ%20Website%20for%20SRA-WHOPARs_1.pdf (Accessed 29 October 2025)

Prepared by:

Name: ..... Job Title: .....

Signature: ..... Date .....

Executive Director: ....
Signature Date