9 October 2017
EMA/CHMP/581887/2016
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on the draft 'Information in the package leaflet for fructose and sorbitol' (EMA/CHMP/460886/2014)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Teva Pharmaceuticals Ltd
2	Novartis Pharma AG
3	Medicines Evaluation Board in The Netherlands (MEB)
4	F. Hoffmann-La Roche Ltd
5	AESGP

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1. General comments – overview

Stakeholder no.	General comment	Outcome (if applicable)
2	Novartis appreciates to comment on this draft information. For Sorbitol E420: The current warning statements in the excipients guidance specifically state the concerned routes of administration, Oral or Parenteral. The new proposed statement wording includes a section for all route of administration, which should be reconsidered for topical Ophthalmic products. It should be clearly stated that the routes of administration relevant to the extra warning statement or exclude specifically topical administration. Rationale: 1. Topical ophthalmic products are administrated for local actions only. And for Sorbitol in these medicinal products to have a systemic effect is considered minimal. 2. Based on most posology for ophthalmic products, the amount of Sorbitol administered topically is very low. 3. It is frequently difficult to calculate the exact amount "mg per volume/dosage" as outlined in the warning statement proposal for Ophthalmic products. Therefore it would be difficult to implement a relevant/meaningful wording to benefit patients.	Accepted. "All routes" replaced by "oral and parenteral" (for both fructose and sorbitol).
3	The MEB has no comments	Noted.
4	The efforts to update the current excipients guideline are appreciated, and proposed revisions are welcomed. This guideline should be updated as new	Noted.

Stakeholder no.	General comment	Outcome (if applicable)
	evidence suggests the need for update.	
4	It is to assume that the proposed updates will be incorporated in the existing guideline. This would result in differences in terms of terminology used for the same condition (e.g. hereditary, genetic and inborn) or different level of details (which could be perceived as more details are needed for those excipients requiring more attention, in fact it is not necessarily the case, e.g. fructose vs. sucrose where sucrose is hydrolysed into glucose and fructose; aspartame vs. phenylalanine; or benzyl benzoate vs. benzoic acid/benzoates).	Accepted. All the statements have been harmonised.
4	It is recommended to include a general requirement in the guideline that the quantity of the excipients per dose unit should be included for cases where toxicity depends on quantity of the excipient. Wording proposal could be as follows: This medicine contains xx mg <excipient> in each <volume/dosage unit>	The comment refers to the main text of the guideline and is not specific to Fructose/Sorbitol. See guideline on EC website.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
6 Fructose (general)	1	**Comments:** When a threshold is based on bodyweight of a patient, a table has to be added to the excipients guideline, connecting bodyweight and age. Which growth standard should be taken as a reference to evaluate the body weight of a child e.g. at the age of 12 years? The WHO weight-for-age reference data only cover the age group 0-10 years but not adolescents. Furthermore, what can be considered as the standard weight (1st centile, 3rd centile or 50th centile, boy, girl)?	Not accepted. The comment is valid, especially for vaccines or other products indicated in children and not dosed per body weight. In that case it is not precise how to judge whether a mg/kg threshold applies for a certain product. However, this issue should be discussed on a case by case basis between companies and the Agency during the authorisation process. It is therefore not considered necessary to add a specific table for reference.
6 Fructose (oral medicines)	1	**Comments:** We propose a threshold of zero for oral formulations. From our point of view, the doctor or pharmacist is the person who should decide whether a patient with HFI can take the medicine. Therefore the threshold of 5 mg /kg/day should be stated in the SmPC as important information for the doctor and pharmacist. A threshold dependent on bodyweight is difficult to handle for oral medicines, as posology is often age-related and not always based on bodyweight. The decision to include the warning might be different from MAH to MAH although the fructose content is the same. This leads to confusion for patients, pharmacists and doctors.	Not accepted. Threshold zero for oral (deletion of 5 mg/kg threshold) would merge warnings and comments on IV and oral which is not adequate, since the intention was to strengthen especially the IV warning.
Fructose -	5	**Proposed change:**	Not accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Oral (formulations in contact with teeth, e.g. liquids, lozenges and chewable tablets)		~~Zero~~ *A threshold could be based on food law principles (e.g. low in sugars is <5g sugar per 100g in EU, so >5g/100g or 2.5ml/100ml, or >5g/2.5ml 'daily exposure' could be used to ensure only products that add a significant level of fructose to the daily diet carry this warning).* **Comment and rationale:** Re-phrasing along these lines is more proportional, and makes it clear that fructose/sugar risks are not heightened vs. normal foods containing sugar.	Although the argument is valid, the risk of fructose/sorbitol from formulations in contact with teeth was not under the scope of the review. Therefore, the threshold and the labelling are kept as they were before.
	5	**Proposed change:** ~~May be harmful to the teeth with chronic use, e.g. for two weeks or more.~~ *Each dose/ampoule/lozenge/chewable tablet contains XXmg fructose. It is important to maintain good dental hygiene as you normally would to reduce the risks of tooth decay with chronic use, e.g. 2 weeks or more.* **Comment and rationale:** Re-phrasing along these lines is more proportional, and makes it clear that fructose/sugar risks are not heightened vs. normal foods containing sugar.	Not accepted. See above.
Fructose (parenteral [other than IV]):	1	**Comments:** We agree with the rationale, but a table as stated above has to be added to the excipients guideline.	Not accepted. The rationale for changing the threshold from 5 mg/kg to zero for oral is unclear, so the threshold has not been changed. See comment above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Additionally, the threshold of 5 mg-/kg/day should be stated in the SmPC as important information for the prescribing doctor. **Proposed change:**	Generally, it is not intended to state thresholds in the SmPC.

Name	Route of Administration	Threshold*	Information for the Package Leaflet	Comments
Fructose	Oral (all formulations) ~~Parenteral (other than IV)~~	~~5 mg/kg/day~~ Zero	If you have been told by your doctor that you have an intolerance to some sugars or if you have been diagnosed with hereditary fructose intolerance, an inborn disorder in which a person lacks the protein needed to break down fructose, contact your doctor or pharmacist before taking/ you are given this medicine.	SmPC proposal: Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product, when a threshold of 5 mg/kg/day is exceeded.
	Parenteral (other than IV)	5 mg/kg/day	If you have been told by your doctor that you have an intolerance to some sugars or if you have been diagnosed with hereditary	SmPC proposal: Patients with hereditary fructose intolerance (HFI) should not

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		fructose intolerance, an inborn disorder in which a person lacks the protein needed to break down fructose, contact your doctor before taking/ you are given this medicine. / take/be given this medicinal product, when a threshold of 5 mg/kg/day is exceeded.	
Page 5 **Fructose** Table	4	**Comments:** Potential inconsistent wording between fructose and sucrose will be introduced by incorporating the revisions into the existing guideline. The wording for sucrose is to be adapted.	Accepted. It is intended to harmonise the wordings.
Page 5 **Fructose** Table row 2 **Same for sorbitol,** page 6, table, row 3	4	**Comments:** For medicines indicated only or also for use in children, the labeling text needs to be revised to reflect this aspect. **Proposed change:** If you **(or your child)** have hereditary fructose intolerance (HFI), a rare generic condition, you (or your child) should not **take**/receive this medicine	Accepted.
Page 5 Table row 6 **Same for sorbitol**,	4	**Comments:** For medicines indicated only or also for use in children, the labeling text needs to be revised to reflect this aspect	Accepted.

<table>
<tr><th>Line no.</th><th>Stakeholder no.</th><th>Comment and rationale; proposed changes</th><th>Outcome</th></tr>
<tr><td>page 6, table, row 7</td><td></td><td>Proposed change:

If you (or your child) have been told by the doctor that you (or your child) have an intolerance to some sugars, or if you have been diagnosed with inhereditary fructose intolerance….

Contact your doctor before taking/receiving ~~be given~~ this medicinal product.</td><td></td></tr>
<tr><td>Sorbitol</td><td>1</td><td>Proposed change:
<table>
<tr><th>Name</th><th>Route of Administration</th><th>Threshold*</th><th>Information for the Package Leaflet</th><th>Comments</th></tr>
<tr><td>Sorbitol E420</td><td>Oral (all formulations)

~~Parenteral (other than IV)~~</td><td>~~5 mg/kg/day~~ Zero</td><td>If you have been told by your doctor that you have an intolerance to some sugars or if you have been diagnosed with hereditary fructose intolerance, an inborn disorder in which a person lacks the protein needed to break down fructose, contact your doctor before taking/ you</td><td>SmPC proposal: Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product, when a threshold of 5 mg/kg/day is exceeded.</td></tr>
</table></td><td>Not accepted.

As above for Fructose</td></tr>
</table>

Line no.	Stakeholder no.	Comment and rationale; proposed changes				Outcome
					are given this medicine.	
			Parenteral (other than IV)	5 mg/kg/day	If you have been told by your doctor that you have an intolerance to some sugars or if you have been diagnosed with hereditary fructose intolerance, an inborn disorder in which a person lacks the protein needed to break down fructose, contact your doctor before taking/ you are given this medicine.	SmPC proposal: Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product, when a threshold of 5 mg/kg/day is exceeded.
			Oral	140 mg/kg/day	May cause gastrointestinal discomfort and mild laxative effect.	