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Information in the package leaflet for fructose and sorbitol in the context of the revision of the guideline on 'Excipients in the label and package leaflet of medicinal products for human use' (CPMP/463/00 Rev. 1)

Draft

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Comments are requested only on the table "*Proposal for updated information in the package leaflet*" using column and row references.

Comments should be provided using this template. The completed comments form should be sent to excipients@ema.europa.eu

Keywords	*Excipients, Package leaflet, Fructose, Sorbitol, E420*

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Executive summary

This document has been written in the context of the revision of the Guideline on 'Excipients in the label and package leaflet of medicinal products for human use' [8].

Fructose and sorbitol are used as excipients in a variety of oral (tablets, capsules, suspensions) and topical formulations (creams, emulsions). Sorbitol (and rarely fructose) is also used as a protein/peptide stabiliser in some medicinal products for parenteral use such as blood products (immunoglobulins) and vaccines.

Since sorbitol is rapidly converted in vivo to fructose by sorbitol dehydrogenase in the liver, systemic safety concerns regarding fructose also apply to sorbitol. Therefore, both substances are combined in one review. In addition, the systemic concerns related to fructose may also apply to other sugars that are metabolised to fructose (e.g. maltitol).

Both fructose and sorbitol are already included in the Annex of the current Guideline with a threshold zero triggering a warning about the risk in case of intolerance to some sugars. Although patients with the rare genetic disorder of hereditary fructose intolerance (HFI) are likely to take into account this warning, there is a concern that it is insufficient for patients who are not aware of their underlying HFI, are unconscious due to an acute medical condition, or are too young for the diagnosis to have been made.

Patients with HFI develop a natural defence mechanism against fructose and sorbitol by vomiting any food containing either of the two substances. Since this defence mechanism is bypassed as soon as fructose or sorbitol is delivered intravenously, a much higher risk is associated with solutions for parenteral (especially intravenous) use.

During the centralised procedure of the intravenous immunoglobulin Flebogamma DIF which contains a high content of sorbitol as an excipient (amount sorbitol administered per single dose: 0.2–2 g/kg) and is indicated for use in children it became obvious that the warning in the Annex of the guideline on Excipients dated 2003 [8] was insufficient.

Subsequently, in the revised guideline for excipients, it is proposed to strengthen the warning for medicinal products containing fructose/sorbitol and given intravenously with regard to the risk for very young children or unconscious patients. This warning provides potential signs of HFI in babies and alerts parents and HCPs that administration in children below 2 years of age with undiagnosed HFI may be fatal. Additional recommendations include the need for a detailed history with regard to HFI symptoms in each patient prior to therapy and the consideration of a contraindication of such medicinal products in children < 2 years of age. It is recognised that the latter has to be judged on a case by case basis, since there might be exceptional cases in which the medicine should still be applicable if necessary (e.g. life-threatening diseases with no alternative treatments).

However, some vaccines and other parenteral biologicals (e.g. monoclonal antibodies) contain very low amounts of sorbitol as an excipient (8–16 mg per dose). They have been administered for a long time without any known incidence of severe event due to HFI, in particular vaccines recommended for children below 2 years of age (MMR, VZV). Therefore the warning for those products should differ from the warning for products administered intravenously.This is why a threshold above zero was derived for oral and parenteral (other than IV) products. By applying this threshold the current misleading warning in the package leaflet of vaccines will not be obligatory any longer.

There is no scientifically established and generally accepted safe dose for patients with HFI. Nevertheless, a threshold dose of 5 mg/kg/day was derived for oral and parenteral (other than IV) products as a limit above which a warning in the PIL is deemed necessary and useful. An oral, subcutaneous or intramuscular dose of 5 mg/kg/day is expected to result in a systemic exposure level (Cmax and AUC) not higher than that reached after an oral dietary intake of 10 mg/kg/day, which is the lowest level of restriction for the oral fructose intake in patients with HFI. This dose level corresponds to 1/8 of the internationally recommended upper level of oral fructose intake in HFI of 40 mg/kg/day and corresponds to 1/50 of the challenge dose of intravenous fructose (0.25 g/kg) applied in the fructose tolerance test which has been used in the past for diagnosis of HFI. This conservative approach was chosen in view of the potentially fatal condition and the fact that the intake from a medicinal product will always be additive to the dietary intake.

Thus, for all oral and parenteral (except IV) products below the threshold of 5 mg/kg/day it is proposed to declare the sorbitol content but not to include a warning. Above this threshold the warning remains as it was before for all administration routes.

A comprehensive review of the gastrointestinal effects of fructose and sorbitol has not been undertaken at this time. The current threshold of 10 g sorbitol for oral products triggering a warning on gastrointestinal discomfort and laxative effects is still considered valid but it is amended to be expressed in mg/kg so it is more appropriate for medicinal products use in children.

A new reference to the potential effects of sorbitol on the bioavailability of other drugs administered concomitantly is given in the comments section.

The current reference regarding diabetes has been deleted, since the small amounts of fructose (or sorbitol) in medicines are not expected to affect the glycaemia in patients with diabetes mellitus.

Proposal for updated information in the package leaflet

[Column and row references to be used for comments]

	A	B	C	D	E
1	**Name**	**Route of Administration**	**Threshold**	**Information for the Package Leaflet**	**Comments**
2	**Fructose**	All routes of administration	Zero	This medicine contains xx mg fructose in each <volume/dosage unit>.	The additive effect of concomitantly administered products containing fructose (or sorbitol) and dietary intake of fructose (or sorbitol) should be taken into account.
3		Intravenous (IV)	Zero	If you have hereditary fructose intolerance (HFI), a rare genetic condition, you should not receive this medicine. In your child (below 2 years of age) HFI may not yet be diagnosed. When receiving medicinal products containing fructose or sorbitol, this may be life-threatening. If you or your child have developed a distaste or get sick or have bloating, stomach cramps or diarrhoea after eating sweet foods you must alert your doctor before you are given this medicine.	Patients with hereditary fructose intolerance (HFI) should not be given this medicine unless strictly necessary. Contraindication should be considered for babies and young children (below 2 years of age) whose hereditary fructose intolerance (HFI) may not yet be diagnosed and may be life-threatening. A detailed history with regard to HFI symptoms has to be taken of each patient prior to being given this medicinal product.
6		Oral (all formulations) 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.	Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.
7		Oral (formulations in contact with teeth, e.g. liquids, lozenges and chewable tablets)	Zero	May be harmful to the teeth with chronic use, e.g. for two weeks or more.	Information to be included when the medicinal product is in contact with teeth (e.g. oral liquids, lozenges or chewable tablets) and may be intended for chronic use, e.g. for two weeks or more.

[Column and row references to be used for comments]

	A	B	C	D	E
1	**Name**	**Route of Administration**	**Threshold**	**Information for the Package Leaflet**	**Comments**
2	**Sorbitol E420**	All routes of administration	Zero	This medicine contains xx mg sorbitol in each <volume/dosage unit> .	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 peroral medicinal products may affect the bioavailability of peroral medicinal products administered concomitantly.
3					
4		Intravenous (IV)	Zero	If you have hereditary fructose intolerance (HFI), a rare genetic condition, you should not receive this medicine. In your child (below 2 years of age) HFI may not yet be diagnosed. When receiving medicinal products containing fructose or sorbitol, this may be life-threatening. If you or your child, have developed a distaste or get sick or have bloating, stomach cramps or diarrhoea after eating sweet foods you must alert your doctor before you are given this medicine.	Patients with hereditary fructose intolerance (HFI) should not be given this medicine unless strictly necessary. Contraindication should be considered for babies and young children (below 2 years of age) whose hereditary fructose intolerance (HFI) may not yet be diagnosed and may be life-threatening. A detailed history with regard to HFI symptoms has to be taken of each patient prior to being given this medicinal product.
5					
6					
7		Oral 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.	Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.
8		Oral	140 mg/kg/day	May cause gastrointestinal discomfort and mild laxative effect.	

Scientific background

1. Characteristics

1.1. Category (function)

Fructose is a monosaccharide.

Sorbitol is a monosaccharide alcohol.

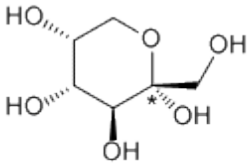
1.2. Physico-chemical Properties

Fructose *(Ph.eur. 01/2008:0188 corrected 6.0)*:

(–)-d-arabino-hex-2-ulopyranose.

(Levulose)

$C_6H_{12}O_6$



and epimer at C*

M_r 180.2

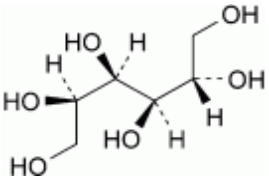
Appearance: white or almost white, crystalline powder. It has a very sweet taste.

Solubility: very soluble in water, soluble in ethanol (96 per cent).

Sorbitol (Ph.eur. 04/2009:0435):

d-Glucitol (d-sorbitol)

$C_6H_{14}O_6$



M_r 182.2

Appearance: white or almost white, crystalline powder.

Solubility: very soluble in water, practically insoluble in ethanol (96 per cent). It shows polymorphism.

1.3. Use in medicinal products

Functions in medicinal products formulations

Fructose and sorbitol are used as excipients in their capacity as sweeteners, flavour constituents, modifier of viscosity, humectant, emollient/plasticisers and protein stabiliser in some medicinal products for parenteral use.

Both sugars are used in high concentrations as active pharmaceutical ingredients in parenteral nutrition formulations (energy source), as laxatives and osmotic diuretics, but this will not be discussed in this document (not in the scope).

Fructose / Sorbitol content in medicinal products for parenteral use

Sorbitol is included in protein/peptide formulations for parenteral use such as intravenous immunoglobulins (IVIGs), monoclonal antibodies, growth factors (e.g. filgrastim) and vaccines (e.g. measles, varicella, yellow fever).

An inquiry about all authorised medicinal products for parenteral use containing sorbitol or fructose as an excipient (centrally in EU and nationally in Germany, France and other MS) revealed that the amount of sorbitol per dose varied considerably between the products. The highest content is found in the intravenous immunoglobulin Flebogamma DIF (50 mg/ml) which corresponds to an amount of 0.2–2 g sorbitol per single dose per kg bodyweight. This would result in a total exposure of 2–20 g/dose in a 10-kg child). The sorbitol content in other biological medicinal products for parenteral use e.g. monoclonal antibodies, growth factors and vaccines is markedly lower, resulting in a total exposure of 2–80 mg/dose. The parenteral vaccines comprise measles and varizella zoster vaccines and combinations thereof (MMR, MMRV), and the yellow fever vaccine Stamaril®. These products contain sorbitol at 8–16 mg/dose and are authorised in children > 9 months. Thus, the parenteral sorbitol dose per kg bodyweight will not exceed 2.4 mg/kg (assumption: lower 3rd centile of weight-for-age in girls at 9 months: 6.6 kg; WHO Multicentre Growth Reference Study Group, 2006).

With regard to fructose, one parenteral product was identified which is an intravenous antimycotic lipopeptide (anidulafungin) formulation (Ecalta®) and contains 204 mg/dose of fructose.

The administration route is mainly subcutaneous and intravenous. All products contain a warning statement that fulfils the requirement of the current Guideline with regard to HFI; however, it is questionable whether the wording for vaccines is meaningful/ appropriate with respect to the age of the vaccinated subjects.

Fructose / Sorbitol content in medicinal products for oral use

In oral use sorbitol can be found in various liquid medicines such as antiallergics (e.g. desloratadine), antiemetics (e.g. ondansetron) and some antibiotics. It is also a common excipient in many types of tablets, e.g. orodispersible tablets (‘melts’). It can also be found in one oral vaccine preparation (Rotarix®).

Fructose is less often used in oral medicines, but can be found in products such as the antivirals Kaletra® (oral liquid) or Isentress® (chewing tablets).

Authorised medicinal products for oral use may contain sorbitol / fructose in the range 2–90% per dosing unit (tablet, millilitre) [19]. Typical products are solutions and suspensions of antibiotics and antitussives, of which some are authorised from birth. The highest sorbitol and fructose exposures are in the range 400–500 mg/kg.

Rotarix® reconstituted suspension, an oral vaccine authorised from birth, contains 13.5 mg/dose sorbitol which normally equals less than 10 mg/kg in a neonate.

2. Pharmaco-toxicological data

An animal model of fructose intolerance in rats exists since 1974 [17].

3. Pharmacokinetics (in humans)

3.1. Absorption

Fructose is the main sugar found in fruit, vegetables and honey. Free fructose, ingested orally either as monosaccharide or enzymatically cleaved from sucrose, is absorbed directly by the intestine. It is transported through the intestinal epithelium by GLUT-5 (passive) and GLUT-2 (active) transporters [3].

Studies indicate that fructose absorption is dose-dependent and facilitated by the simultaneous ingestion of glucose [11]. Saturation of absorptive capacity is reached with doses of about 0.5 g/kg body weight, above which a significant proportion of subjects show signs of fructose malabsorption [18]. Plasma fructose concentration time courses are available from 19 healthy subjects after peroral intake of 50 g fructose [21], and from 8 healthy adults after a test meal of 0.5 g/kg fructose [20]. Both showed a peak in plasma fructose after 30 min (tmax).

Sorbitol is incompletely absorbed at a rate much slower than that of fructose, and seems dose and concentration dependent. When sorbitol is given as a single oral dose, the intestinal absorptive capacity has been estimated to be no more than 2–10 g; furthermore, it has been suggested that, when given together, sorbitol and fructose compete for absorption [13].

There are no data on rate and extent of absorption (i.e. bioavailability) of fructose or sorbitol when administered subcutaneously or intramuscularly, e.g. after administration as excipients in vaccines or other biologicals.

3.2. Metabolism

Fructose is transported into the liver by the GLUT2 transporter. Uptake of fructose by the liver is not regulated by insulin. (However, insulin is capable of increasing the abundance and functional activity of GLUT5 in skeletal muscle.) The first step in the metabolism of fructose is the phosphorylation of fructose to fructose 1-phosphate by fructokinase, thus trapping fructose for metabolism in the liver. Fructose 1-phosphate then undergoes hydrolysis by fructose 1,6-bisphosphate aldolase (aldolase B) to form DHAP and glyceraldehydes. This enzyme is defective in hereditary fructose intolerance, HFI (see chapter on clinical safety data).

Sorbitol is rapidly converted to fructose by sorbitol dehydrogenase in the liver. Together with aldose reductase, it provides a way for the body to produce fructose from glucose without using ATP. Sorbitol dehydrogenase uses NAD+ as a cofactor; its reaction is sorbitol + NAD+ --> fructose + NADH + H+. A zinc ion is also involved in catalysis. The organs that use it most frequently include the liver and seminal vesicle.

4. Clinical safety data

4.1. Hereditary Fructose Intolerance (HFI)

Background

HFI is a hereditary autosomal recessive deficit in fructose 1,6-bisphosphate aldolase (aldolase B), the main enzyme responsible for hepatic metabolism of fructose. It is expressed in the liver, small intestine, and proximal renal tubule where it facilitates assimilation of dietary fructose by catalysing the cleavage of fructose-1-phosphate [1]. A lack of functional aldolase B leads to an accumulation of toxic fructose 1-phosphate in liver cells, ultimately resulting in hepatic decompensation.

Patients with HFI develop a natural defence mechanism against fructose and sorbitol by vomiting any food containing either of the two substances. This defence mechanism is bypassed as soon as fructose or sorbitol is delivered intravenously. Therefore, a much higher risk is associated with solutions for parenteral use.

The worldwide incidence of HFI at birth is estimated at 1:20.000–1:30 000. The prevalence of HFI in adults is unknown.

HFI has to be distinguished from DFI (dietary fructose intolerance, fructose malabsorption), which is an uncomfortable but benign condition. It occurs when the amount of fructose consumed is more than the small intestines can absorb. Unabsorbed fructose acts as an osmotic load which can cause diarrhoea and other gastrointestinal symptoms [9].

Diagnosis

Clinical

The disorder is not apparent until the infant is weaned and fed with formula, juice, fruits, or baby foods or honey that contain fructose. In young children a spontaneous aversion for fructose develops and the onset of symptoms may be delayed when parents scrupulously respect the child's tastes for food and do not impose fructose-containing products rejected by the child.

Biopsy and testing

A formal diagnosis can also be made by a dosage of fructose 1-phosphate aldolase on tissue obtained by hepatic biopsy. Detection can also be made by a fructose tolerance test. This test induces within 30 min. hypoglycaemia, hypophosphoremia, and hyperuricaemia with signs of hepatocellular insufficiency. However, this test may be dangerous, and many clinicians prefer to perform a hepatic biopsy.

Genetic

The ALDOB gene (on Chr. 9) of the enzyme fructose 1 phosphate aldolase (or aldolase B) has been sequenced and a direct diagnosis is possible by using DNA prepared from nucleated blood cells. Four identical aldolase B enzymes need to form a tetramer to work. More than 50 mutations in the ALDOB gene have been found to cause HFI. Most of these mutations replace single amino acids in the aldolase B enzyme and result in the production of an enzyme with reduced function. Three specific mutations account for 95% of patients of European origin. A mutation found in approximately half of people with HFI replaces the amino acid alanine with the amino acid proline at position 149 in the enzyme (written

as Ala149Pro or A149P). This mutation alters the 3-dimensional shape of the enzyme making it difficult for the aldolase B enzymes to form tetramers and thus metabolise fructose.

Symptoms

Clinical symptoms usually include vomiting, anorexia, gastro-intestinal disorders, apathy, height and weight retardation and hepatomegaly. Forced ingestion of a large amount of fructose may lead to acute hepatic decompensation, with major hepatocellular insufficiency, haemorrhagic syndrome and jaundice. The reason for the severe adverse events with infusion of fructose solution, including death, is not hypoglycaemia but the intracellular accumulation of fructose 1-phosphate which is highly toxic.

Biochemical signs are postprandial hypoglycaemia, hypophosphatemia, hyperlactacidemia and hyperuricaemia. Prolongation of coagulation time, increased hepatic enzymes and increased bilirubin are also often present. Methionine and plasma tyrosin are often elevated. A proximal and distal renal tubulopathy is frequent.

Treatment

The treatment consists in complete withdrawal of fructose, sorbitol and saccharose, which can lead to resolution of hepatic disorders. In case of suspected fructose intolerance during infusion of fructose or sorbitol, infusion has to be stopped immediately, normal glycaemia has to be re-established and organ function has to be stabilised by intensive care procedures.

Safety data

If fructose (or sorbitol) containing infusions are given in hospitals to children not yet diagnosed with HFI, acute hepatic and renal insufficiency can develop, followed by death within a few days.

Babies and young children represent the population with the highest risk, as HFI may not yet have been diagnosed, but inadvertent administration of parenteral fructose (sorbitol) solutions can also have life-threatening consequences in adult HFI patients.

On 2nd March 2001 a “Benefit-risk evaluation of fructose and sorbitol-containing solutions for parenteral use” was performed by Daniel Brasseur and Xavier Kurz following the death of an 18-month-old child who had been administered a fructose-containing solution (IV) [10]. In the literature up to 1993 23 cases were reported, whereof 17 were fatal (73%). Not all 17 case reports had information on dosing. However, three adult patients died after receiving ~ 25–50 g of sorbitol (in one case an infusion over 10 h). The report concludes: “An excessive amount of fructose or sorbitol is not necessary for a fatal outcome”. Death typically occurred within 3–10 days after the first fructose or sorbitol administration as a consequence of severe renal and liver failure.

Although this assessment was done with regard to the fructose and sorbitol-containing solutions for parenteral nutrition in which the sugars act as active substances and are present in high concentrations, the conclusions of the assessment had an impact on the EU authorisation procedure for Flebogamma DIF, a sorbitol-containing intravenous immunoglobulin.

Flebogamma DIF (Grifols) solutions for infusion contain 50 mg sorbitol/ml as an excipient and 50 or 100 mg IgG/ml as the active substance. According to the recommended dosing, a child with e.g. Kawasaki’s disease weighing 10 kg would require 20 g IgG which would translate to 20 g of intravenous sorbitol. This is in the order of magnitude of the fatal doses for HFI adults mentioned above.

Thus, in the updated SmPC for Flebogamma DIF children under 2 years of age were excluded from the indications and a statement was added: “In babies and young children (aged 0-2 years) hereditary

fructose intolerance (HFI) may not yet be diagnosed and may be fatal, thus, they must not receive this medicinal product."

Furthermore, the following statement was added under Section 4.4:

> *Sorbitol*
>
> *Each ml of this medicinal product contains 50 mg of sorbitol. Patients with rare hereditary problems of fructose intolerance must not take this medicine.*
>
> *In persons more than 2 years old with HFI, a spontaneous aversion for fructose-containing foods develops and may be combined with the onset of symptoms (vomiting, gastro-intestinal disorders, apathy, height and weight retardation). Therefore a detailed history with regard to HFI symptoms has to be taken of each patient prior to receiving Flebogamma DIF.*
>
> *In case of inadvertent administration and suspicion of fructose intolerance the infusion has to be stopped immediately, normal glycaemia has to be re-established and organ function has to be stabilized by means of intensive care.*
>
> *Interferences with determination of blood glucose levels are not expected.*

4.2. Gastrointestinal effects of oral use

The current version of the guideline acknowledges the potential laxative effect of oral sorbitol and includes a threshold of 10 g triggering a warning that the product "may have a mild laxative effect". Although this limit might be suitable for adults, it is probably less relevant for children of low age and weight. It is also known that children can be more sensitive to this effect compared to adults, although the variability may be high [12]. Furthermore, the gastrointestinal effects are not limited to laxation but also include other signs of GI discomfort (e.g. bloating, cramps).

4.3. Potential pharmacokinetic interaction

In addition, it has been described in the literature that some liquid oral formulations containing sorbitol may affect the bioavailability of other drugs administered concomitantly. For example, lamivudine bioavailability is affected by sorbitol contained in the oral solution of abacavir (340 mg sorbitol/ml) and the oral suspension of nevirapine (162 mg sorbitol/ml) [7]. Also risperidone bioavailability (i.e. Cmax and AUC) is affected in some subjects when sorbitol amounts as low as 7.5 and 60 mg are given [16].

4.4 Diabetes

Fructose in medicines represents a small fraction of fructose intake from the diet (less than 10%) in terms of calorific value. Furthermore, it is not expected to affect the glycaemia in patients with diabetes mellitus. Therefore, adding such information in the package leaflet is not considered to be relevant. A similar rationale applies to sorbitol.

5. Safety information relevant for the package leaflet

5.1. Hereditary Fructose Intolerance (HFI)

Summary of concerns

Although the risk of administration of products containing fructose or sorbitol to patients with HFI has been reduced by the current warning statement, there is a concern that this warning is insufficient for the patients in whom HFI has not yet been diagnosed and particularly the small children. This concern triggered the rewording of the Flebogamma DIF product information (see above). Therefore, in the revised guideline, a new strengthened and more detailed warning was derived from this rewording.

In parenteral products (see 1.3.) the total sorbitol exposure in adults varies by a factor of 70,000 (e.g. Scintimun®: 2 mg/dose versus Flebogamma DIF: 140 g/dose), while monoclonal antibodies, growth factors and vaccines contain very low amounts of sorbitol (2–80 mg/dose). Particularly in the case of vaccines, which are applied only once (or twice) in lifetime and are administered subcutaneously (or intramuscularly), the absorption of sorbitol is much slower than in the IV administration; therefore it is questionable whether a special warning with regard to HFI is appropriate.

The parenteral vaccines containing sorbitol are administered in children > 9 months. At that age HFI is more likely to have been diagnosed, but if the child is not yet weaned this might still not be the case. However, the maximum parenteral sorbitol dose per kg bodyweight is estimated to be 2.4 mg/kg (see 1.3). Considering that proposed new strengthened warning should alert parents and HCPs that administration may be fatal in children < 2 years of age, this is not appropriate for these vaccines recommended at the age of < 2 years. Moreover, a warning does not enhance the decision-making process for parents or healthcare professionals as children are too young to be diagnosed. Furthermore, these vaccines have been administered for a long time without any incidence of severe event due to fructose intolerance.

Then, the next question would be whether a threshold can be identified below which oral and parenteral (other than IV) administered fructose/sorbitol is tolerated by an HFI patient at different ages or whether medicinal products for children < 2 years should be absolutely fructose/sorbitol-free.

Non-toxic dose

Since the molecular weight of fructose and sorbitol is quite similar (see 1.2), in all calculations below they are regarded as equivalent.

Fatal parenteral administrations of fructose and sorbitol cause acute hepatorenal failure associated with bleeding. Adult patients have died after receiving 25 g of sorbitol intravenously [10].

In the fructose tolerance test which has been used in the past for diagnosis of HFI, patients are challenged IV with fructose 0.25 g/kg body weight. As a result glycogenolysis is inhibited and gluconeogenesis is impaired [4]. Diagnosis by a fructose tolerance test leads to the same acute symptoms as HFI and can be life threatening. It can be deduced that this dose can definitely be regarded as toxic and should therefore be above a potential threshold.

Patients with HFI are treated by strict fructose-free diet. Although the precise daily limit of oral fructose is unknown a restriction to less than 40 mg/kg/day is recommended [10]. Mock et al. demonstrated in two unrelated boys with HFI (5.3 and 3.8 years of age) with isolated growth retardation in infancy that a more stringent restriction of dietary fructose to less than 40 mg fructose per kg body weight daily lead to an increase in growth velocity to the 75th and 97th percentile,

respectively [15]. When the restriction of dietary fructose was relaxed (from 10 to 250 mg/kg/day), neither of the boys had symptoms, hypoglycaemia, or evidence of hepatic or renal dysfunction. However, both had sustained hyperuricaemia and hyperuricosuria and increases in the plasma concentration and urinary excretion of magnesium [4]. The authors do not exclude that chronic ingestion of even trace amounts of these sugars lead to long-term effects.

The Scientific Panel on Dietetic Products, Nutrition and Allergies of EFSA published in 2005 an opinion paper on a request from the Commission related to the evaluation of fructose for labelling purposes [5]. They stated that the spectrum of individual fructose tolerance in HFI appears to depend on age (infants being more sensitive than adults) and on the respective gene mutation and that there are no scientifically established and generally accepted triggering doses for patients with HFI.

However, a publication by Barshop et al. 2003 indicates that short-term (2 days) dietary intake of 4.7 mg of fructose/kg/day was safe and well tolerated among individuals with diagnosed HFI [2]. Five subjects with HFI (ages 14–52 years; 4 males, 1 female) participated in a prospective, non-randomised open challenge with FOS at 6 g/m^2/d for 2 days. A female infant (5 months) with resolved neonatal hepatitis was also studied. Diet records were maintained for the 48-hr period and analysed for dietary fructose. Tolerance was assessed through evaluation of serum AST, ALT, GGT, glucose, bilirubin, uric acid, phosphorus, and electrolytes, upon initiation and at 12-hr intervals during the challenge. Blood chemistry values were within normal ranges and did not change appreciably during the study period, except for two patients with slight elevations of uric acid. One subject reported gastric discomfort on day 2 of the FOS challenge. These data suggest that approximately 4.7 mg fructose/kg bw/day for 2 days is safe and well tolerated among individuals with diagnosed HFI.

Conclusion and recommendation / Derivation of a threshold

There is no scientifically established and generally accepted safe dose for patients with HFI. However, an internationally accepted safety recommendation restricts the oral fructose intake in HFI below 40 mg/kg/day. The most stringent restriction of the oral fructose intake in HFI described in the literature is 10 mg/kg/day [4]. This level was chosen for the calculation of a threshold. This conservative approach was chosen as the intake from a medicinal product will always be additive to the dietary intake.

At this recommended level of oral intake (10–40 mg/kg) the absorption capacity of the intestines is probably not reached (0.5 g/kg BW, see PK section 3.1), hence 100% bioavailability can be assumed.

After subcutaneous or intramuscular administration of vaccines systemic bioavailability of sorbitol is considered kinetically comparable to the oral administration with regard to the velocity and amount of absorption of fructose/sorbitol. However, since there are no PK data on subcutaneous or intramuscular absorption of fructose/sorbitol available, it cannot be excluded that absorption from these routes might be even faster than the oral absorption and Cmax reached in plasma after subcutaneous administration might be higher than after an oral application of the same dose/kg. Therefore, the orally “tolerable” dose of 10 mg/kg/day was divided by a factor of 2 to be safely applicable also for the s.c./i.m. route. Thus, a threshold dose of 5 mg/kg/day for oral and parenteral (other than IV) products was chosen which is expected to result in a systemic exposure level not higher than that reached after an oral dietary fructose intake of 10 mg/kg/day. This threshold is not regarded as “safe daily dose” but as limit above which a detailed warning in the PIL is deemed necessary and useful.

This threshold would be in line with the observation of the well tolerated oral dose of 4.7 mg/kg/day observed in the small challenge study by Barshop et al. [2] which included one child of 5 months of age.

Furthermore, the oral Rotavirus vaccine Rotarix® is administered twice to newborns from 6 weeks up to 16 weeks of age, when HFI is probably not yet diagnosed. It contains 13.5 mg/dose which equals to 4.5 – 6.8 mg/kg in a 2-3 kg newborn. There are no indications that this level gave rise to adverse events or even death related to HFI.

Therefore, in the revised annex of the guideline, for all oral and parenteral (except IV) products below this threshold, the declaration of the sorbitol content without a warning is considered appropriate. Above this threshold the warning remains as it was before as it is regarded as sufficient for the safe use of orally administered drugs, while a new intravenous threshold zero is introduced, triggering the inclusion of a more detailed warning and a recommendation for interdicting the use in children below 2 years of age. It is recognised that the latter has to be judged on a case by case basis, since there might be exceptional cases in which the medicine should still be applicable if necessary (e.g. life-threatening diseases with no alternative treatments).

5.2. Laxative and gastrointestinal effects

When taken orally in larger amounts sorbitol (and to a less extent fructose) can also cause laxative effects and gastrointestinal discomfort. Sorbitol is often used in formulations intended for children and infants and young children might be more sensitive to this effect [13].

The current (adult) threshold of 10 g of sorbitol triggering a warning on potential laxative effect is considered correct but it is proposed to express it in mg/kg so it is more appropriate for medicinal products used in children. Therefore a weight adjusted threshold of 140 mg/kg (equivalent of 10 g/70 kg) is proposed for all patients.

5.3. Potential interaction

There is some recent evidence in the literature that perorally administered sorbitol can affect the bioavailability of other concomitant peroral drugs (see 4.3). A sorbitol amount as low as 7.5 mg is accused, corresponding to 0.107 mg/kg body weight in a 70 kg adult. Therefore, a statement pointing out the potential effects of sorbitol on the bioavailability of other drugs administered concomitantly was added in the comments section of sorbitol which refers to all routes of administration at threshold zero.

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Annex 1 - Information in the package leaflet as per 2003 Guideline

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Fructose	Oral Parenteral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product	SPC proposal for section 4.3: Patients with rare hereditary problems of fructose intolerance should not take this medicine.
		5 g	Contains x g fructose per dose. This should be taken into account in patients with diabetes mellitus.	
	Oral liquids, lozenges and chewable tablets	Zero	May be harmful to the teeth	Information to be included only when the medicinal product may be intended for chronic use, e.g. for two weeks or more.

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Sorbitol E420	Oral Parenteral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.	SPC proposal: Patients with rare hereditary problems of fructose intolerance should not take this medicine.
	Oral	10 g	May have a mild laxative effect Calorific value 2.6 kcal/g sorbitol	