Recommendations:

- Confirm the complete list of excipients of each medicine before administration: All excipients are mandatory in a technical file and leaflet. Consult your pharmacist or European Medicine Agency (EMA) Online Drug Information: http://www.ema.europa.eu/ema/

- Avoid medicines with contraindicated excipients.

- Those in which the amount of sorbitol or fructose they generate is unknown or may not be very high, it is necessary to assess the individual risk/benefit and find alternatives available in the market. The tolerance in HFI patients depends on individual characteristics, the amount of fructose/sorbitol released and/or absorbed and the purity and amount of the excipient containing the medicament. But the tolerance is always small for this reason it is important to avoid them whenever there are alternatives.

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Note: This guide is informative to facilitate decision making. This document does not replace the information in the label or leaflet, legislation or current recommendations for patients with HFI. The authors are not responsible for the misuse that can be made of it.

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HEALTHCARE PROFESSIONAL INFORMATION: MEDICATIONS IN HEREDITARY FRUCTOSE INTOLERANCE (HFI)

1. HFI is an autosomal recessive metabolic disease, due to Aldolase B deficiency, an enzyme responsible for fructose metabolism in the liver (to a lesser extent in the kidney and intestine).

2. Symptomatology:

- Acute intoxication (intake of large amounts of fructose: 4-6 g/kg/day): rapid and violent abdominal pain, vomiting, somnolence, shock, severe hepatic and renal dysfunction, with or without hypoglycemia and even death.

- Chronic intoxication (prolonged exposure to minor amounts of fructose: ≤1.2 g/kg/day): poor feeding, occasional but recurrent vomiting, hepatomegaly, edema and/or ascites, and failure of thrive.

3. Treatment: It is necessary to eliminate all sources of fructose, sucrose, sorbitol and tagatose. The daily intake of fructose should not exceed 20-40 mg/kg/day in children, although there is no agreement on the amount of fructose that is considered safe.

4. Medications: There are excipients in medicines that may have or generate fructose. We do not know their exact metabolism or the amount of fructose or sorbitol that they release in many of them, so there is controversy with their recommendations in patients with HFI.

Information for HFI Spanish association:

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ALLOWED excipients in HFI patients:

Acesulfame
Alitame
Aspartame
Cyclamate
Erythritol
Glucose, dextrinomaltose
Glucose syrup*
Steviol glycosides
Neohesperidine dihydrochalcone
Saccharin
Sucralose **
Taumatina
Xylitol

* Caution: Glucose syrup may contain fructose.
** Caution: Sucralose may contain small amounts of sucrose. It is obtained from sucrose (purity ≥ 98%)

CONTRAINDICATED excipients in HFI patients:

Inverted sugar
Fructose
High Fructose Corn Syrup (HFCS)
Oral sucrose*
Sorbitol or sorbitol syrup
Sucromalt
Tagotose

* Intravenous sucrose: 70-90% of the infused dose is eliminated unchanged in urine as disaccharide (higher interindividual variability). There is not data of use in HFI patients.

- Other excipients:

• Aromas and flavorings may contain sugars in their composition. If they contain excipients as fructose, sucrose, inverted sugar, sorbitol, maltitol, lactitol or isomaltitol they must be indicated in the package and leaflet. But it is recommended to consult with the medicine's proprietary laboratory.

• Polysorbates or Tween 80: They are sorbitol esters that can release some amounts of sorbitol. Cases of typical symptoms of intoxication have been reported in patients with HFI. Use with caution.

• Polydextrose: It is a molecule formed by glucose polysaccharides and small amounts of sorbitol (10%). Use with caution.

Other excipients that should **BE ADMINISTERED WITH CAUTION** (Avoid them whenever there are alternatives) depending on the individual tolerance, purity and quantity present in the medication (release variable amounts of fructose/sorbitol). It is necessary to establish risk/benefit individually:

Excipients	Metabolism	Comments
Inuline, oligofructose, fructo-oligosaccharides.	Fructose polysaccharidese. It is not degraded by digestive enzymes but at acid pH (stomach) small amounts of fructose could be released (8% in 2 hours).	Also commercial products may contain free fructose (1.3%) and sucrose (3.4%)
Isomaltitol	Mix of sorbitol (<6%), mannitol (<3%), maltitol, and glucose-mannitol. Its disaccharides are hydrolyzed by 10%. The released sorbitol is partially absorbed[1].	
Maltitol syrup.	Mix of sorbitol, maltitol and hydrogenated polysaccharides. About 40-50% is hydrolyzed. The released sorbitol is partially absorbed[1].	
Lactitol	Galactose and sorbitol disaccharide. 2% is hydrolyzed and the released sorbitol is partially absorbed[1].	Contraindicated as laxative (one dose have 10 grams of lactitol)
Maltitol	Glucose and sorbitol disaccharide. 40% is hydrolyzed and the released sorbitol is partially absorbed[1].	
Mannitol	It is obtained by the hydrogenation of fructose. It is absorbed by 25-65%. Its metabolism is unknown: 7-10% is oxidized in the liver, it is unknown whether to fructose or to other metabolites.	Oral: use with caution. Intravenous: NOT RECOMMENDED due to the large amount of mannitol infused and doubts about its metabolism.

[1] Absorption data are based on insulinemia and glycaemia, the amount of glucose released is rapidly and completely absorbed, but not that of sorbitol which is partially absorbed (about 25%). It is unknown exactly how much sorbitol they can provide.