RECOMMENDATIONS:

- Confirm the full list of excipients for each drug before administration in labelling and package leaflet: All excipients are compulsorily listed in the labeling and package leaflet. Check in: https://checkmedicine.aaihf.com/

- Avoid all those contraindicated. In case of oral and parenteral fructose and sorbitol (except intravenous), according to the current legislation products below the threshold of 5 mg/kg/day it will be declared the sorbitol and fructose content but not to include a warning (EMA / CHMP / 302620/2017).

- Flavourings: they may contain sugars in their composition. If they contain contraindicated excipients (fructose, sucrose, invert sugar, sorbitol, maltitol, lactitol or isomaltitol) they must indicate this on the labeling and package leaflet.

- Those in which the amount of sucrose, fructose or sorbitol it contains is low, individually assess the risk/benefit and the alternatives available on the market. Its tolerance will depend on the individual characteristics of the patient, the amount of fructose/sorbitol released and/or absorbed and the purity, amount of the excipient that the drug contains and the severity of the patient's clinical situation. Avoid them whenever there are alternatives.

Bibliography:

- Sweeteners in patients with HFI. Acta Pediatr Esp. 2014; 72: 15-23
- Drug syrups: Errors in drug labels with possible consequences in patients with hereditary fructose intolerance. An Pediatrics. 2017.
- Excipients in the labeling and package leaflet of medicinal products for human use. EMA / CHMP / 302620/2017. October 2017.
- Standards of identity and purity of sweeteners used in food products. Royal Decree 299/2009 of March 6. BOE, nº 68 (03-20-2009).
- Joint FAO / WHO Expert Committee on Food Additives (JECFA).
- European Food Safety Authority (EFSA).
- Food and Drug Administration (FDA).

Note: This guide is informative to facilitate decision making. In no case will it replace the information in the labeling and package leaflet, legislation or current recommendations for patients with HFI. The authors are not responsible for any misuse that may be made of it.

INFORMATION FOR THE HEALTHCARE PROFESSIONAL: DRUGS IN HEREDITARY FRUCTOSE INTOLERANCE (HFI) OR HEREDITARY FRUCTOSEMIA

1. What is the HFI? It is an autosomal recessive hereditary disease, due to a deficiency in the enzymatic activity of Aldolase B, an enzyme responsible for metabolizing fructose mainly in the liver (to a lesser extent in the kidney and intestine).

2. Symptoms:

- Acute poisoning (intake of large amounts of fructose: 4-6 g/kg/day): rapid and violent appearance of abdominal pain, vomiting, drowsiness, shock, severe liver dysfunction and kidney dysfunction, with or without hypoglycemia.

- Chronic intoxication (prolonged exposure to minor amounts of fructose: ≤ 1-2 g/kg/day): difficulties in feeding, occasional but recurrent vomiting, hepatomegaly, edema and/or ascites and failure to thrive.

3. Treatment: Elimination of all sources of fructose, sucrose, sorbitol and tagatose from the diet. 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 or on the liberalization of the diet in older children and teenagers.

4. Medications: There are excipients that contain or are metabolized to fructose in their composition. For many of them, their exact metabolism or the amount they provide of fructose or sorbitol is unknown. These excipients can be present in syrups, tablets and capsules, and in intravenous presentations (immunoglobulins, monoclonal antibodies, growth factors, vaccines, antibiotics/antifungals, etc.)

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Asociación de Afectados por Intolerancia Hereditaria a la Fructosa

1. **PERMITTED** excipients in patients with HFI:

Acesulfame, alitame, aspartame
Cyclamate
Erythritol
Glucose, dextrinomaltose (corn sugar)
Glucose syrup * (corn syrup)
Steviol glycosides
Neohesperidine-dihydrochalcone
Saccharin
Sucralose **
Thaumatina
Xylitol (birch sugar)

* Caution: may contain fructose. Errors have been detected in in the labeling and package leaflet where they indicated glucose syrup and it was fructose syrup or maltitol. Confirm with the laboratory.

** Caution: may contain small amounts of sucrose. Obtained from sucrose (purity ≥ 98%)

2. **CONTRAINDICATED** excipients in HFI patients.
Assess risk/benefit individually in case of emergency:

CARBOHYDRATES:	
Invert sugar	Glucose and fructose syrup.
Fructose	Metabolism via Aldolase B.
Sucrose (ORAL)	Glucose and fructose disaccharide, is hydrolyzed by intestinal disaccharidases.
Sucromalt	Mixture of fructose, leucrose (isomer of sucrose that hydrolyzes to fructose and glucose), oligosaccharides of glucose.
Tagatose	Fructose enantiomer, 20% absorbed is metabolized by the same metabolic pathway as fructose (Aldolase B)
POLYALCOHOLS:	
Isomaltitol	Sorbitol (<6%), mannitol (<3%), maltitol, and glucose-mannitol mixture. Its disaccharides are hydrolyzed by 10%. The released sorbitol is partially absorbed.
Lactitol	Galactose-Sorbitol disaccharide. It is hydrolyzed by 2% and the sorbitol released is partially absorbed. Contraindicated as a laxative (one sachet provides 10 grams of lactitol)
Maltitol	Glucose-sorbitol disaccharide. It is hydrolyzed by 40% and the sorbitol released is partially absorbed.
Sorbitol	It is absorbed ± 25%, the part absorbed is metabolized to fructose.
OTHERS:	
Honey	Contains fructose.
Other syrups	Raspberry, elderberry or thyme syrup: Contains fructose.

3. Other excipients (assess benefit/risk individually):

- **Intravenous sucrose**: 70-90% of the infused dose is eliminated unchanged in urine as disaccharide (inter-individual variability). There are no data in HFI patients.

- **Mannitol:** polyol obtained from fructose, 25-65% is absorbed, but it is unknown whether 7-10% could be transformed into fructose in the liver. It is not recommended in patients with HFI, where benefit/risk must be assessed, especially when large amounts are administered by the INTRAVENOUS ROUTE.

- **Sorbitol esters (Span) or sucrose esters**: They are esters of sorbitol or sucrose that can release small amounts of sucrose or sorbitol.

- **Polysorbates (Tween):** Cases of typical symptoms of intoxication have been described in patients with HFI. They are sorbitol esters and polyoxyethylenated fatty acids where the bond between sorbitol and ethylene oxide cannot be hydrolyzed, so the release of sorbitol would not occur.

- **Polydextrose**: Molecule formed by glucose polysaccharides and small amounts of sorbitol (10%), although it is practically not metabolized in the gastrointestinal tract.

- **Caramel colouring:** It is obtained by heat treatment of carbohydrates (glucose, sucrose, invert sugar, etc.) Its composition is unknown.

- **Inulin, oligofructose, fructo-oligosaccharides:** Fructose polysaccharide. It is not degraded by digestive enzymes. At acidic (stomach) pH, small amounts of fructose (8% in 2 hours) may be released. Also, commercial products may contain free fructose (1.3%) and sucrose (3.4%)

Check if the medicines are suitable according to your intolerance and excipients on the page:
https://checkmedicine.aaihf.com/