Safety of vaccines administration in hereditary fructose intolerance

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Abstract

Patients with hereditary fructose intolerance need to follow a life-long fructose dietary and drug restriction to prevent symptoms of intoxication. Concerns about vaccines administration have been manifested overtime, for the risk of a life-threatening acute intoxication. For this reason, at Ospedale Pediatrico Bambino Gesù we performed a deepen research from open sources, datasheets and Pharmaceutical Companies informations from the most common Italian and European vaccines, which are carried out in infancy and childhood. As a safe threshold of 2.4 mg/kg/dose was recently established for oral and parenteral (other than i.v.) route, the manuscript clarifies the safe administration of majority of vaccines in patients with hereditary fructose intolerance.

Keywords: Hereditary fructose intolerance, Fructose, Sorbitol, Sucrose, Vaccines

Hereditary fructose intolerance (HFI, OMIM 229,600) is an autosomal-recessive disorder with a prevalence of 1:23,000, caused by deficiency of aldolase B, the main enzyme responsible for hepatic metabolism of fructose. The signs and symptoms upon introduction of fructose-containing foods include abdominal pain, nausea, recurrent vomiting, hypoglycemia and failure to thrive. Besides hypoglycemia, metabolic disturbances such as lactic acidemia, hypophosphatemia, hyperuricemia and hypermagnesemia are observed in case of acute fructose intoxication. Parenteral intravenously administration of fructose, sorbitol, or sucrose may cause death for severe hypoglycemia, acute hepato-renal failure associated with bleeding and jaundice and must be rigorously avoided [1]. For this reason, the diagnostic challenge with i.v. fructose 0.25 g/kg was abandoned and substituted by the molecular analysis. Also the diagnostic oral load of fructose 1 g/kg is no longer recommended as deemed life threatening as well.

Many individuals with HFI exhibit a self-imposed aversion to sweet foods, sufficiently to prevent an acute intoxication. However, prolonged fructose intake leads to poor feeding, vomiting, failure to thrive, hepatomegaly, liver and renal tubular dysfunction that might lead to irreversible liver and kidney damage [1, 2]. Upon dietary restriction of fructose, symptoms resolve and normal growth and development are achieved. Therefore, individuals with HFI need to be treated life-long with a fructose-restricted diet. They should be aware of the presence of fructose in certain medicinal formulations and such medications should be avoided. Particularly, concerns about oral or parenteral vaccines administration have been manifested overtime, because they contain amounts of sorbitol or sucrose or other analogous sugars.

However, there is no scientifically established and generally accepted safe dose for patients with HFI despite the fact that, at least in childhood, the intake of fructose should not be determined by subjective tolerance. As a matter of fact, the spectrum of individual fructose tolerance in HFI appears to depend on age (infants being more sensitive than adults), beyond the respective gene mutation [3].

Scientific evidences are very poor. One paper advises that short-term (2 days) oral administration of 4.7 mg/kg of sorbitol may be safe for patients with HFI [4]. However, other studies have shown that even short-term administration of sorbitol may cause hypoglycemia and other metabolic disturbances [5]. Therefore, further research is needed to establish safe doses of sorbitol and other sugars in patients with HFI.
kg/day of fructose was safe and well tolerated among 5 individuals (aged 14–52 years) with diagnosed HFI [4], with normal blood chemistry and only a slight elevation of uric acid in two patients. An internationally accepted safety recommendation restricts the oral fructose intake below 40 mg/kg/day, whereas the more stringent fructose restriction reported is 10 mg/kg/day [1, 5]. This level of 10 mg/kg/day was chosen from the European Medicine Agency (EMA) [5] for the calculation of a threshold to generate informations for a package leaflet regarding fructose and sorbitol used as excipients in medicinal products for human oral use. This conservative approach was chosen as the intake from a medicinal product will always be additive to the dietary intake. Although at this level the intestinal absorption capacity (0.5 g/kg) is probably not reached, there are no data on PK from subcutaneous or intramuscular absorption of fructose and sorbitol. However, it can be assumed that parenteral administration might be faster and consequently plasma concentration might be higher. Therefore, the orally tolerable dose of 10 mg/kg/day was divided by a factor of 2 to be safely applicable also for s.c./i.m route, expecting for a parenteral (other than i.v.) dose of 5 mg/kg/day a similar systemic exposure level (Cmax and AUC) than an oral fructose intake of 10 mg/kg/day [5].

Thus, for all oral and parenteral (other than i.v., for which the threshold is zero) products below the threshold of 5 mg/kg/day it has been proposed to declare the sorbitol content but not to include a warning [5]. This threshold is not regarded as a safe daily dose but as a limit above which a detailed warning in the leaflet is deemed necessary and useful. Indeed, above this threshold the warning remained for all administration routes. Nonetheless, in some vaccines a warning within the datasheet states “Do not administer in subjects with HFI”, even when the content of sorbitol or sucrose does not exceed this limit.

The need to avoid any hazardous exposure to fructose contained in vaccines collides with the need of immunization for the most vulnerable age group from severe infections. Furthermore, some vaccines have been administered for a long time without any incidence of severe events due to HFI, for instance in patients with a delayed diagnosis. For these reasons, at Ospedale Pediatrico Bambino Gesù of Rome, we performed a deep research from open sources (Pubmed, Cochrane) and datasheets available from the most common vaccines which are carried out in infancy (0–1 years), early (2–5 years) and mid childhood (6–11 years) in Italy and in the other European Countries where vaccines have the same international authorization commerce (Table 1). We collaborated with our hospital Pharmacy and the Pharmaceutical Companies to outline the exact amount of fructose, sucrose, sorbitol and other fructose analogues when not reported in the datasheets. We performed a deep research through the open sources in Italian databases Codifa (https://www.codifa.it) and AIFA (https://www.agenziafarmaco.gov.it/content/vaccini), and in the European Medicines Agency (https://www.ema.europa.eu/en/medicines).

We obtained the following informations:

- Rotarix pre-established oral suspension (clear and colourless liquid, the only formulation commercially available in Italy) and Rotateq contain sucrose above 1000 mg/dose, therefore they are contraindicated in subjects with HFI
- Rotarix white powder and solvent for oral suspension, commercially available in other European Countries, containing sucrose 9 mg and sorbitol 13.5 mg, can be administered in HFI children with a weight > 9.3 kg (2.4 mg/kg/dose)
- Imovax polio, Vaxelis, Enderix B, HBVAXPRO, Twinrix, Hibrix, Menjugate, Pneumovax, Synflorix, Anatetall, Imovax tetano, Boostrix, Diftetall, Triaxis, Tribaccine do not contain fructose nor analogues sugars, therefore they can be safely administrated in subjects with HFI
- M-M-RVAXPRO, Proquad, Varilrix, Hexyon, Priorix and Priorix tetra contain sorbitol up to 16 mg + sucrose or mannitol traces, therefore, according to a recent document of Istituto Superiore di Sanità di Italy [6], they can be administered with reasonable safety, whenever a threshold of 2.4 mg/kg/dose will not be exceeded (assumption: lower than 3rd percentile of weight-for-age in females at 9 months: 6.6 kg according to WHO Multicentre Study Growth Reference Study Group, 2006). Thus, in accordance with the Italian vaccinal calendar, the administration of M-M-RVAXPRO, Proquad and Varilrix can be done despite the warning in the datasheet stating “Do not administer in subjects with HFI”
- All other vaccines contain fructose and analogues in traces up to 10 mg. Therefore, according to the above recommendations [6] they can be administered with reasonable safety from infancy. Furthermore, the monoclonal antibody Palivizumab (Synagis, AbbVie), used for Respiratory Syncytial Virus’ immunization, contains mannitol traces and can be safely administered in preterm newborns.

In summary, according to the recommendation of Istituto Superiore di Sanità di Italy [6], considering a limit of 2.4 mg/kg/dose as a safe threshold for oral and parenteral (s.c./i.m.) route, majority of vaccines can be safely
| Vaccine name                          | Vaccine components                  | Fructose analogues dose | Marketing authorization holder | Member State where product is authorised                       |
|--------------------------------------|-------------------------------------|-------------------------|-------------------------------|---------------------------------------------------------------|
| Antihaemophilus B vaccine            | ACTHIB-intramuscular or subcutaneous use |                          | Sanofi Pasteur               | IT                                                            |
|                                      | ANTIHAEMOPHILUS B                   | Sucrose                 |                              |                                                               |
|                                      | HIBERIX-intramuscular use           | ANTIHAEMOPHILUS B       | GlaxoSmithKline              | IT                                                            |
|                                      |                                     | None                    |                              |                                                               |
|                                      | The antihaemophilus B component is also present in the following vaccines |                         |                              |                                                               |
|                                      | *HEXYON                             |                         |                              |                                                               |
|                                      | *INFANRIX HEXA                       |                         |                              |                                                               |
| Antihepatitis vaccine B              | ENGERIX B-intramuscular use         | ANTIHEPATITIS B         | GlaxoSmithKline              | BG, DE, DK, EL, ES, FR, IT, NL, PT, SE                        |
|                                      | HVBAXPRO-intramuscular use          | ANTIHEPATITIS B         | Sanofi Pasteur               | BG, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IT, LT, LV, MT, NL, PT, RO, SE, SI, SK |
|                                      | The hepatitis B component is also present in the following vaccines |                         |                              |                                                               |
|                                      | TWINRIX adults intramuscular use    | ANTIHEPATITIS B—ANTIHEPATITIS A | GlaxoSmithKline              | BG, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IT, LT, LV, MT, NL, PT, RO, SE, SI, SK |
|                                      | TWINRIX pediatric-intramuscular use | ANTIHEPATITIS B—ANTIHEPATITIS A | GlaxoSmithKline              | BG, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IT, LT, LV, MT, NL, PT, RO, SE, SI, SK |
|                                      | The hepatitis B component is also present in the following vaccines |                         |                              |                                                               |
|                                      | *HEXYON                             |                         |                              |                                                               |
|                                      | *INFANRIX HEXA                       |                         |                              |                                                               |
| Antimeasles vaccine                  | PRIORIX-subcutaneous use            | ANTIMEASLES—ANTIRUBELLA—ANTI-MUMPS | GlaxoSmithKline              | BG, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IT, LT, LV, MT, NL, PL, PT, RO, SE, SI, SK |
|                                      | M-M-RVAXPRO-intramuscular or subcutaneous use | ANTIMEASLES—ANTIRUBELLA—ANTI-MUMPS | Sorbitol 9 mg Mannitol | MSD Vaccines                                                   | AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, IE, IS, IT, HR, HU, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK |
|                                      | The anti-measles component is also present in the following vaccines |                         |                              |                                                               |
|                                      | *HEXYON                             |                         |                              |                                                               |
|                                      | *INFANRIX HEXA                       |                         |                              |                                                               |
| Antimeningococcal B vaccine          | BEXSERO-intramuscular use           | ANTI-MENINGOCOCCAL B    | GlaxoSmithKline              | BG, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IT, LT, LV, MT, NL, PL, PT, RO, SE, SI, SK |
|                                      | TRUMENBA-intramuscular use          | ANTI-MENINGOCOCCAL B    | Pfizer Europe                | BG, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IT, LT, LV, MT, NL, PL, PT, RO, SE, SI, SK |
| Antimeningococcal C vaccine          | MENUJUGATE-intramuscular use        | ANTI-MENINGOCOCCAL C    | GlaxoSmithKline              | IT                                                            |
|                                      | NEISVAC-C-intramuscular use         | ANTI-MENINGOCOCCAL C    | Pfizer S.r.l                 | IT                                                            |
| Vaccine name                  | Vaccine components                                                                 | Fructose analogues dose | Marketing authorization holder | Member State where product is authorised |
|------------------------------|-------------------------------------------------------------------------------------|-------------------------|---------------------------------|------------------------------------------|
| **The anti-meningoococcal component C is also present in the following vaccines** |                                                                                      |                         |                                |                                          |
| MENVEO-intramuscular use      | CONJUGATED ANTI-MENINGOCOCCUS A, C, W135, Y                                         | Sucrose                 | GlaxoSmithKline                 | BG, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IT, LT, LV, MT, NL, PL, PT, RO, SE, SK |
| NIMENRIX-intramuscular use    | CONJUGATED ANTI-MENINGOCOCCUS A, C, W135, Y                                         | Sucrose                 | Pfizer S.r.I                    | BG, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IT, LT, LV, MT, NL, PL, PT, RO, SE, SI, SK, UK |
| **Antipapilloma virus**       |                                                                                      |                         |                                |                                          |
| GARDASIL 9-intramuscular use  | HUMAN ANTIPAPILLOMAVIRUS (human types 6, 11, 16, 18, 31, 33, 45, 52, 58)            | Polysorbate 80          | MSD Vaccines                    | AT, BE, BG, CZ, CY, DE, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK |
| **Antipneumococcal vaccine**  |                                                                                      |                         |                                |                                          |
| PNEUMOVAX-intramuscular or subcutaneous use | ANTI-PNEUMOCOCCICAL                                                                    | none                    | Sanofi Pasteur                  | IT                                         |
| PREVENAR 13-intramuscular use | ANTI-PNEUMOCOCCICAL                                                                    | Polysorbate 80          | Pfizer S.r.I                    | BG, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IT, LT, LV, MT, NL, PL, PT, RO, SE, SK |
| SYNFLORIX-intramuscular use   | ANTI-PNEUMOCOCCICAL                                                                    | none                    | GlaxoSmithKline                 | BG, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IT, LT, LV, MT, NL, PL, PT, RO, SE, SK |
| **Antipolio vaccine**         |                                                                                      |                         |                                |                                          |
| IMOVAX POLIO-intramuscular or subcutaneous use | ANTIPOLIO                                                                           | None                    | Sanofi Pasteur                  | IT                                         |
| **The polio component is also present in the following vaccines** |                                                                                      |                         |                                |                                          |
| HEXYON-intramuscular use      | ANTIPOLIO—ANTIDIPHTERIA—ANTITETANUS—ANTIPERTUSSIS—ANTHAEMOPHILUS B—ANTHEPATITIS B  | Saccarose 10.6 mg       | Sanofi Pasteur                  | AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SI, SK, UK |
| INFANRIX HEXA-intramuscular use| ANTIPOLIO—ANTIDIPHTERIA—ANTITETANUS—ANTIPERTUSSIS—ANTHAEMOPHILUS B—ANTHEPATITIS B  | Polysorbate 80 contained in the medium excipient 199 | GlaxoSmithKline                 | BG, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SI, SK, UK |
| POLIOBOOSTRIX intramuscular use | ANTIPOLIO—ANTIDIPHTERIA—ANTITETANUS—ANTIPERTUSSIS—ANTHAEMOPHILUS B—ANTHEPATITIS B  | Polysorbate 80 contained in the medium excipient 199 | GlaxoSmithKline                 | AT, BG, DE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK |
| POLIONFANRIX intramuscular use | ANTIPOLIO—ANTIDIPHTERIA—ANTITETANUS—ANTIPERTUSSIS—ANTHAEMOPHILUS B—ANTHEPATITIS B  | Polysorbate 80 contained in the medium excipient 199 | GlaxoSmithKline                 | BE, DE, EE, EL, FI, FR, HR, HU, IE, IT, LT, LU, LV, MT, NL, NO, PL, PT, SE, SK, UK |
| REVAXIS-intramuscular or subcutaneous use | ANTIPOLIO—ANTIDIPHTERIA—ANTITETANUS—ANTIPERTUSSIS—ANTHAEMOPHILUS B—ANTHEPATITIS B  | Polysorbate 80 contained in the medium excipient 199 | Sanofi Pasteur                  | AT, BE, DE, ES, FR, IE, IT, LU, NL, PT, UK |
| TRIAXIS POLIO—intramuscular use | ANTIPOLIO—ANTIDIPHTERIA—ANTITETANUS—ANTIPERTUSSIS—ANTHAEMOPHILUS B—ANTHEPATITIS B  | Polysorbate 80 contained in the medium excipient 199 | Sanofi Pasteur                  | IT                                         |
| TETRAVAC-intramuscular use    | ANTIPOLIO—ANTIDIPHTERIA—ANTITETANUS—ANTIPERTUSSIS—ANTHAEMOPHILUS B—ANTHEPATITIS B  | Polysorbate 80 contained in the medium excipient 199 | Sanofi Pasteur                  | AT, BE, DE, DK, EE, EL, ES, FI, FR, IE, IS, IT, LU, LV, NO, PT, SE, UK |
### Table 1 (continued)

| Vaccine name | Vaccine components | Fructose analogues dose | Marketing authorization holder | Member State where product is authorised |
|--------------|--------------------|-------------------------|--------------------------------|------------------------------------------|
| VAXELIS—intramuscular use | ANTIPOLIO—ANTIDIPHTERIA—ANTITETANUS—ANTIPERTUSSIS—ANTHAEMOPHILUS B—ANTIHEPATITIS B | None | MCM Vaccine | BG, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IT, LT, LV, MT, PL, PT, RO, SE, SI, SK |
| Antirotavirus vaccine | | | | |
| ROTATEQ—oral use | ANTIROTAVIRUS pentavalent, live, reasorting | Sucrose 1,080 mg Polysorbate 80 | Sanofi Pasteur | BG, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IT, LT, LV, MT, NL, PL, PT, RO, SE, SI, SK |
| ROTARIX—oral suspension | ANTIROTAVIRUS live, attenuated | Sucrose 1.073 mg | GlaxoSmithKline | BG, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IT, LT, LV, MT, NL, PL, PT, RO, SE, SI, SK |
| ROTARIX—powder and solvent for oral suspension | ANTIROTAVIRUS live, attenuated | Sucrose 9 mg Sorbitol 13.5 mg | GlaxoSmithKline | BG, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IT, LT, LV, MT, NL, PL, PT, RO, SE, SI, SK |
| Antitetan vaccine | | | | |
| ANATETALL—intramuscular use | ANTITETANUS adsorbed | None | GlaxoSmithKline | DE, HU, IT, SI |
| IMOVAX TETANO—intramuscular or subcutaneous use | ANTITETANUS | None | Sanofi Pasteur | CZ, DE, FR, HR, IT, MT, NO, RO, SK |
| The antitetan component is also present in the following vaccines | | | | |
| BOOSTRIX—intramuscular use | ANTITETANUS—ANTIDIPHTERIA—ANTIPERTUSSIS | None | GlaxoSmithKline | AT, BE, BG, CY, DE, DK, EL, ES, FI, FR, HU, JE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, SE, SI, SK, UK |
| DIFTETALL—intramuscular use | ANTITETANUS—ANTIDIPHTERIA | None | Astro-Pharma | IT |
| INFANRIX DTPA—intramuscular use | ANTITETANUS—ANTIDIPHTERIA—ANTIPERTUSSIS | Polysorbate 80 | GlaxoSmithKline | IT |
| TRAIXIS—intramuscular use | ANTITETANUS—ANTIDIPHTERIA—ANTIPERTUSSIS | None | Sanofi Pasteur | BE, DK, EL, ES, FI, FR, JN, IS, LU, SE, NL, NO |
| TRIBACCINE—intramuscular use | ANTITETANUS—ANTIDIPHTERIA—ANTIPERTUSSIS | None | AJ Vaccines A/S | IT |
| *HEXYON | | | | |
| *INFANRIX HEXA | | | | |
| *POLIOBOOSTRIX | | | | |
| *POLIOINFANRIX | | | | |
| *REVAXIS | | | | |
| *TETRAVAC | | | | |
| Antivariella vaccine | | | | |
| VARILRIX—subcutaneous use | ANTICHICKENPOX | Sorbitol 6 mg Mannitol | GlaxoSmithKline | IT |
| VARVAX—intramuscular or subcutaneous use | ANTICHICKENPOX | Sucrose | MSD Italia S.r.l | IT |
Table 1 (continued)

| Vaccine name | Vaccine components | Fructose analogues dose | Marketing authorization holder | Member State where product is authorised |
|--------------|-------------------|-------------------------|--------------------------------|----------------------------------------|
| PRIORIX TETRA subcutaneous use | ANTICHRICKENPOX—ANTIMEASLES—ANTIRUBELLA—ANTIMUMPS | Sorbitol 14 mg Mannitol Polysorbate 80 contained in the medium excipient 199 | GlaxoSmithKline | BG, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IT, LT, LV, MT, NL, PL, PT, RO, SE, SI, SK |
| PROQUAD-intramuscular or subcutaneous use | ANTICHRICKENPOX—ANTIMEASLES—ANTIRUBELLA—ANTIMUMPS | Sorbitol 16 mg Sucrose Polysorbate 80 contained in the medium excipient 199 | MSD Italia S.r.l | BG, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IT, LT, LV, MT, NL, PL, PT, RO, SE, SI, SK |

The table displays the different types of vaccines which are commercialized in Europe and their amount of fructose analogues content.

AT Austria, BE Belgium, BY Bulgaria, CY Cyprus, CZ Czech Republic, DE Germany, DK Denmark, EE Estonia, EL Greece, ES Spain, FI Finland, FR France, HR Croatia, IE Ireland, IS Iceland, LT Lithuania, LU Luxembourg, HU Hungary, MT Malta, NL Netherlands, NO Norway, PL Poland, PT Portugal, RO Romania, SI Slovenia, SK Slovakia, IT Italy, LV Latvia, SE Sweden, UK United Kingdom

3 Medium excipient 199, a complex of amino acids, mineral salts, vitamins, polysorbate 80 and other substances diluted in water for injections.
administered in infants and children with HFI. The vaccines M-M-RVAXPRO and Proquad can be administered after 9 months at a weight > 6.5 kg. Rotarix white powder and solvent for oral suspension can be administered at a weight > 9.3 kg. The only contraindicated vaccines in HFI are Rotarix pre-established oral suspension and Rotateq.

Abbreviations
AIFA: Italian Agency of Drug; AUC: Area under the curve; Cmax: Maximum concentration; EMA: European Medicine Agency; HFI: Hereditary fructose intolerance; i.m.: Intramuscular; i.v.: Intravenous; PK: Pharmacokinetics; s.c.: Subcutaneous; WHO: World Health Organization.

Author contributions
AM made substantial contributions to the conception and design of the work, to the acquisition, analysis, and interpretation of data; she have drafted the work or substantively revised it. AS made contribution to the acquisition, analysis, and interpretation of data. TC made contribution to the acquisition of data and revised the manuscript. CD made contribution to the acquisition of data, have drafted the work or substantively revised it. All authors have approved the submitted version and have agreed both to be personally accountable for the author’s own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Reference
1. Cox TM. Aldolase B and fructose intolerance. FASEB J. 1994;8:62–71.
2. Mock DM, Perman JA, Thaler M, Morris RC Jr. Chronic fructose intoxication after infancy in children with hereditary fructose intolerance. A cause of growth retardation. N Engl J Med. 1983;309:764–70.
3. Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the evaluation of fructose for labelling purposes. EFSA J. 2005;279:1–8. http://www.efsa.eu.int/science/nda/nda_opinions/catindex_en.html.
4. Banhoph B, Nyhan WL, Philippe HS, Endres W, Tolan DR, Clemens RA. Fructo-oligosaccharide tolerance in patients with hereditary fructose intolerance. A preliminary nonrandomized open challenge short-term study. Nutr Res. 2003;23:1003–11.
5. EMA 2016 Committee for Human Medicinal Products (CHMP). 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). London: EMA; 2016. (EMA/CHMP/460886/2014). https://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/05/WC500206001.pdf.
6. Gallo G, Mel R, Ros E, Filia A (Ed.) Guida alle controindicazioni alle vaccinazioni (aggiornamento 2018). Roma: Istituto Superiore di Sanità, 2019 (Rapporti ISTISAN 19/3).

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