ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TOT'HEMA, oral solution in ampoule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Iron ..... 50.00 mg
Corresponding to ferrous gluconate hydrate ..... 399.73 mg

Manganese ..... 1.33 mg
Corresponding to manganese gluconate ..... 10.78 mg

Copper ..... 0.70 mg
Corresponding to copper gluconate ..... 5.00 mg

For a 10 ml ampoule.

Excipients with known effect: glucose (99 mg/10 ml), sucrose (3000 mg/10 ml), ethanol (108 mg/10 ml), sodium benzoate (20 mg/10 ml).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution in ampoule.

TOT'HEMA is a clear dark brown liquid. The presence of a fine precipitate is possible.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Curative treatment of iron deficiency anaemia in adults, children and infants.

Preventive and curative treatment of iron deficiency in pregnant women, premature infants, twins or babies born to a mother with iron deficiency, when an adequate dietary iron intake cannot be ensured.

4.2. Posology and method of administration

Posology

One ampoule contains 50 mg of elemental iron.

Curative treatment of iron deficiency anaemia:

For infants from 1 month and children: 3 mg of elemental iron/kg/day, without exceeding 60 mg.

For adults: 100 to 150 mg of elemental iron per day, i.e. 2 to 3 ampoules per day, in a single or divided dose.

For patients with renal impairment:

No dosage adjustment is generally necessary in patients with renal impairment (see section 4.4).

For patients with hepatic impairment:

No dosage adjustment is generally necessary in patients with hepatic impairment (see section 4.4).

Preventive and curative treatment of iron deficiency:

For pregnant women: 50 mg of elemental iron per day, i.e. 1 ampoule per day during the last 2 trimesters of pregnancy (or from the 4th month).

Treatment duration

Treatment must last long enough to correct anaemia (Hb, MCV) and/or restore iron stocks (serum ferritin, transferrin saturation coefficient), which, in adults, are 600 mg for women and 1200 mg for men.

Anaemia due to iron deficiency: haemoglobin levels should be checked 4 weeks after treatment initiation. The timing of further checks will depend upon the degree of anaemia. The treatment duration is generally 3 to 6 months depending on the depletion of iron stocks, to be eventually prolonged if the cause of anaemia is not under control Treatment must be continued for 3 additional months after normalisation of the haemoglobin level.

Method of administration

Oral use.

Shake the ampoule before use.

After breaking the ampoule from both sides, its content must be diluted in water (sweetened or not).

This medicine will be administrated preferably before meals, but the time of administration and sometimes the dose can be adapted according to digestive tolerance.

4.3. Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Iron overload due to increased intestinal absorption or altered iron metabolism (e.g. haemochromatosis, thalassemia, refractory anaemia, aplastic anaemia, sideroblastic anaemia) or due to excessive parenteral entry (e.g. repeated or chronic blood transfusions).
- Non-iron deficiency anaemias (e.g. haemolytic anaemia, megaloblastic anaemia, anaemia of inflammation).
- Wilson's disease.

4.4. Special warnings and precautions for use

Special warnings

- This medicine is not recommended as a treatment for hyposideremia associated to inflammatory syndromes.
- Iron supplementation should be carried out along with treatment of iron loss cause, whenever it can.
- Accidental high intake can lead to intoxication that can be fatal, especially in children (see section 4.9).
- TOT'HEMA must not be administered intravenously.
- Accidental aspiration during the administration of the oral solution of iron can cause granulomas, lesions or necrosis of the bronchial mucosa which may result in coughing, haemoptysis and/or bronchostenosis (even if aspiration happened days to months before these symptoms occurred). Elderly patients and patients who have difficulties swallowing are particularly at risk of aspiration. Patients should seek medical attention in case of suspected aspiration.
- Patients with fructose intolerance, glucose malabsorption or sucrase-isomaltase insufficiency (rare hereditary diseases) should not take this medicine.
- The presence of glucose and of sucrose may be harmful to the teeth in case of prolonged use (at least 2 weeks).
- This medicine contains 108 mg of alcohol (ethanol) per ampoule of 10 ml. The amount of ethanol in 10 ml of this medicine is equivalent to less than 3 ml beer or 2 ml wine. The small amount of alcohol in this medicine will not have any noticeable effects.
- This medicine contains less than 1 mmol sodium (23 mg) per ampoule of 10 ml, that is to say essentially 'sodium-free'.
- This medicine contains 20 mg of sodium benzoate per ampoule of 10 ml. Sodium benzoate may increase jaundice (yellowing of the skin and eyes) in new-born babies (up to 4 weeks old).
- Patients with liver dysfunction including alcoholic liver disease, non-alcoholic fatty liver disease, and viral hepatitis should be carefully treated with TOT'HEMA as well as patients with existing gastrointestinal diseases such as chronic inflammatory bowel disease, bowel stenoses, diverticula, gastritis, gastric and intestinal ulcers.

- Patients with renal impairment may have an increase of their iron requirement and require supplementation to treat iron deficiency or anaemia. In non-dialysis patients with renal impairment, especially stages 2-3, oral iron supplementation is possible if well tolerated (see section 4.2). In dialysis patients with chronic renal impairment (stage 5D), and potentially in patients in stages 3-5, iron supplementation should be administered intravenously. TOT'HEMA must not be administered intravenously.
- Concomitant intake of large quantities of tea or coffee inhibits the absorption of iron (see section 4.5).

Precautions of use

- The prevention of infantile deficiency is based on the early introduction of a diversified diet.
- According to data published in the literature, the lining of the stomach and gastrointestinal tract of patients receiving iron-based treatments may be pigmented, which may interfere with gastrointestinal surgery (see section 4.8).

4.5. Interaction with other medicinal products and other forms of interaction

Combinations not recommended

+ Iron (salts) (injectable route):

Lipothymia or even shock due to the rapid release of iron from its complex form and transferrin saturation.

Combinations with precaution for use

+ Cyclines (oral route):
Decreased gastrointestinal absorption of cyclines and iron.
Administration of iron salts with cyclines should be separated (by more than 2 hours, if possible).

+ Fluoroquinolones:
Decreased gastrointestinal absorption of fluoroquinolones.
Administration of iron salts with fluoroquinolones should be separated (by more than 2 hours, if possible).

+ Topical gastrointestinal medicines, antacids and adsorbants:
Decreased gastrointestinal absorption of iron.
As a precaution, these topicals or antacids should be taken away from any other medication (by more than 2 hours, if possible).

+ Bisphosphonates (oral use):
Decreased gastrointestinal absorption of bisphosphonates.
Administration of iron salts should be separated from that of bisphosphonates (by at least 30 minutes to more than 2 hours, if possible, depending on the bisphosphonate).

+ Calcium:
Decreased gastrointestinal absorption of iron salts.
Iron salts should be taken between meals and not with calcium.

+ Cholestyramine:
Decreased gastrointestinal absorption of iron salts.
Iron salts should be taken 1 to 2 hours before or 4 hours after ingestion of cholestyramine.

+ Entacapone:
Decreased gastrointestinal absorption of entacapone and iron due to chelation of iron by entacapone.
Administration of iron salts with entacapone should be separated (by more than 2 hours, if possible).

+ Integrase inhibitors (HIV):
Decreased gastrointestinal absorption of integrase inhibitors.
Administration of iron salts with antiretrovirals should be separated (by more than 2 hours, if possible).

+ Bictegravir:
Decreased gastrointestinal absorption of bictegravir by almost two third in case of simultaneous ingestion or on fasted conditions.
Take bictegravir at least 2 hours before iron salts, or at the same time during a meal.

+ Trientine:

Decreased concentrations of serum iron.
Administration of iron salts with trientine should be separated.

+ Carbidopa, levodopa:
Decreased gastrointestinal absorption of carbidopa and levodopa.
Administration of iron salts with carbidopa and levodopa should be separated (by more than 2 hours, if possible).

+ Methyldopa:
Decreased gastrointestinal absorption of methyldopa (formation of complexes).
Administration of iron salts with methyldopa should be separated (by more than 2 hours, if possible).

+ Penicillamine:
Decreased gastrointestinal absorption of penicillamine.
Administration of iron salts with penicillamine should be separated (by more than 2 hours, if possible).

+ Thyroid hormones:
Decreased gastrointestinal absorption of thyroid hormones.
Administration of iron salts with thyroid hormones should be separated (by more than 2 hours, if possible).

+ Strontium:
Decreased gastrointestinal absorption of strontium.
Administration of iron salts with strontium should be separated (by more than 2 hours, if possible).

+ Zinc:
Decreased gastrointestinal absorption of zinc.
Administration of iron salts with zinc should be separated (by more than 2 hours, if possible).

+ Food:
Phytic acids (whole grains), vegetables, polyphenols (tea, coffee, red wine), calcium (milk, dairy products) and some proteins (eggs) significantly impair the absorption of iron.

Administration of iron salts should be separated from these foods by more than 2 hours (if possible).

Combination to be taken into account

+ Acetohydroxamic acid:

Decreased gastrointestinal absorption of the two medicinal products by iron chelation.

4.6. Fertility, pregnancy and lactation

Pregnancy

There are limited data on the use of iron in the 1st trimester of pregnancy to assess the risk of malformation.

Data from clinical trials do not show any impact of iron supplementation during pregnancy on birth weight, prematurity and neonatal death.

Studies on animals do not show any toxicity on reproduction (see section 5.3).

Therefore, TOT'HEMA can be used during pregnancy, if needed.

Breast-feeding

Iron is present in small amounts in breast milk. Its concentration is independent of maternal contributions. Therefore, no effects are expected on breastfed new-borns/infants.

Fertility

No effects on male or female fertility were observed in animal studies (see section 5.3).

4.7. Effects on ability to drive and use machines

TOT'HEMA has no or a negligible influence on the ability to drive and use machines.

4.8. Undesirable effects

The adverse reactions observed during clinical studies conducted with TOT'HEMA and the adverse reactions collected during post-marketing surveillance are listed according to the MedDRA system organ classification and by frequency using the following categories: very common (≥ 1/10), common (≥ 1/100

to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), unknown (cannot be estimated from the available data).

MedDRA System Organ Class	Common	Frequency not known (cannot be estimated from the available data)
Immune system disorders		Hypersensitivity, anaphylactic reaction
Gastrointestinal disorders	Constipation, diarrhoea, heartburn, nausea, vomiting, black stools, abdominal distension, abdominal pain	Gastrointestinal irritation, gastritis, gastrointestinal pseudomelanosis* Stained teeth**
Skin and subcutaneous tissue disorders		Rash, pruritus, urticaria, angioedema, allergic dermatitis

*According to data published in the literature, the lining of the stomach and gastrointestinal tract of patients receiving iron-based treatments may be pigmented, which may interfere with gastrointestinal surgery.

** Brown or black spots on teeth are reversible upon treatment discontinuation.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system: Agence nationale de sécurité du médicament et des produits de santé (ANSM) and network of Centres Régionaux de Pharmacovigilance - Website: www.signalement-sante.gouv.fr.

4.9. Overdose

Cases of overdose with iron salts have been reported, particularly in small children, by accidental ingestion. Ingestion of oral dose of 20 mg elemental iron/kg body weight or more can lead to intoxication symptoms. Ingestion of more than 60 mg/kg can result in severe toxicity. The equivalent of 200 to 250 mg elemental iron/kg is considered potentially fatal. Acute iron poisoning can occur into four stages:

• In the first phase, which occurs up to 6 hours after oral ingestion, gastrointestinal toxicity, notably vomiting and diarrhoea, predominates. Other effects may include cardiovascular disorders such as hypotension, metabolic changes including acidosis and hyperglycaemia, and CNS depression ranging from lethargy to coma. Patients with only mild to moderate poisoning do not generally progress past this first phase.

• The second phase, which is not always seen, may occur 6 to 24 hours after ingestion and is characterised by a temporary remission or clinical stabilisation.

• In the third phase, 12 to 48 hours after ingestion, gastrointestinal toxicity recurs together and can be associated with the following effects: shock, metabolic acidosis, severe lethargy or coma, hepatic necrosis and jaundice, hypoglycaemia, coagulation disorders, oliguria or renal failure, and possible myocardial dysfunction.

• The fourth phase may occur several weeks after ingestion and is characterised by gastrointestinal obstruction and possibly late hepatic damages.

Treatment should be instituted as soon as possible. Depending on serum iron concentrations, use of a chelating agent is recommended (i.e. deferoxamine).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: ANTIANEMIC PREPARATIONS, ATC code: B03AE10.

Mechanism of action

Iron is an essential mineral nutrient that plays a key role in many physiological functions such as oxygen transport, ATP production, DNA synthesis and electron transport.

Iron is the central atom of the haem groups embedded in haemoglobin and is therefore essential for erythropoiesis.

Iron preparations allow to eliminate iron deficiency in the body and prevent it from occurring if there is an increased need for iron, or insufficient iron stocks.

5.2. Pharmacokinetic properties

Absorption

Iron absorption is an active process that occurs mainly in the duodenum and proximal jejunum. Absorption is increased when iron stores are decreased.

Copper may positively influence the transport of iron in enterocytes.

Iron absorption may be affected by concomitant use of certain foods, beverages or the co administration of certain medicinal products (see sections 4.4 and 4.5).

Distribution

In the body, iron is stored mostly in the bone marrow (erythroblasts) and erythrocytes. Iron is stored in a complex as ferritin in the liver, spleen and bone marrow. In the bloodstream, iron is transported by transferrin, mainly to the bone marrow where it is incorporated into haemoglobin.

Biotransformation

Iron, copper and manganese are metal ions, not metabolized by the liver.

Elimination

Average iron excretion in healthy subjects is estimated at about 1 mg/day.

The main routes of elimination are the gastrointestinal tract (enterocyte shedding, haem degradation from erythrocyte extravasation), the urogenital tract and the skin.

The major route of manganese and copper excretion is via the bile.

5.3. Preclinical safety data

For each active substance, non-clinical data reveal no special hazard for humans at the proposed doses based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Glycerol, liquid glucose, sucrose, citric acid, sodium citrate, sodium benzoate, polysorbate 80, caramel colouring (E150c)*, tutti frutti flavouring**, purified water.

*Composition of caramel colouring (E150c): glucose, ammonium hydroxide.

**Composition of tutti frutti flavouring: isoamyl acetate, isoamyl butyrate, benzaldehyde, ethyl methylphenylglycidate, gamma undecalactone, ethylvanilline, alcohol, water.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

2 years.

6.4. Special precautions for storage

Do not store above 30°C.

6.5. Nature and contents of container

Oral solution in ampoule of 10 ml (brown glass).

Box of 20 ampoules.

6.6. Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

LABORATOIRE INNOTECH INTERNATIONAL
22 AVENUE ARISTIDE BRIAND
94110 ARCUEIL
FRANCE

8. MARKETING AUTHORISATION NUMBER(S)

- 34009 310 731 3 0: 10 ml in ampoule (brown glass); box of 20 ampoules.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 February 1993

Date of latest renewal: 11 February 2013

10. DATE OF REVISION OF THE TEXT

10 August 2022

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.