For the use only of registered medical practitioners or a hospital or a laboratory

Iron(III) Isomaltoside 1000 Solution for Injection/Infusion 100 mg/ml

AMERICAN ISOTOSE 1G
Injection

1. GENERIC NAME: Iron (III) Isomaltoside 1000 Solution for Injection/Infusion 100mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:
Each ml contains:
Iron (III) Isomaltoside 1000
Equivalent to Elemental Iron 100 mg
Excipients q.s.

3. DOSAGE FORM AND STRENGTH
Solution for Injection/Infusion 100mg/ml, Iron (III) Isomaltoside 1000

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Iron (III) Isomaltoside 1000 solution for injection/infusion is indicated for the treatment of iron deficiency in the following conditions:
- When oral iron preparations are ineffective or cannot be used
- Where there is a clinical need to deliver iron rapidly

The diagnosis must be based on laboratory tests.

4.2 Posology and method of administration
Posology
The posology of Iron (III) Isomaltoside 1000 solution for injection/infusion follows a stepwise approach: [1] determination of the individual iron need and [2] calculation and administration of the iron dose(s). The steps can be repeated after [3] post-iron repletion assessments.

Step 1: Determination of the iron need:
The iron need can be determined using either the simplified Table (i) or the Ganzoni formula below (ii).
The iron need is expressed in elemental iron.

i. Simplified Table:
Table 1. Simplified Table

Hb (g/dl)	Hb (mmol/l)	Patient with Body Weight <50 kg	Patients with Body Weight of 50 kg to <70 kg	Patient with Body Weight ≥70 kg
⩾10	⩾6.2	500 mg	1000 mg	1500 mg
<10	<6.2	500 mg	1500 mg	2000 mg

Table 2. Ganzoni formula
Iron need = Body weight$^{(A)}$ x (Target Hb$^{(D)}$ – Actual Hb)$^{(B)}$ x 2.4 + Iron for iron stores$^{(C)}$
[mg iron] [kg] [g/dl] [mg iron]

(A) It is recommended to use the patient's ideal body weight for obese patients or pre-pregnancy weight for pregnant women. For all other patients use actual body weight. Ideal body weight may be calculated in a number of ways e.g. by calculating weight at BMI 25 i.e. ideal body weight = 25* (height in m)^2

(B) To convert Hb [mM] to Hb [g/dl] you should multiply Hb [mM] by factor 1.61145

(C) For a person with a bodyweight above 35 kg, the iron stores are 500 mg or above. Iron stores of 500 mg are at the lower limit normal for small women. Some guidelines suggest using 10-15 mg iron /kg body weight.

(D) Default Hb target is 15 g/dl in the Ganzoni formula. In special cases such as pregnancy consider using a lower haemoglobin target.

iii. Fixed iron need:
A fixed-dose of 1000 mg is given and the patient is re-evaluated for further iron needs according to "Step 3: Post-iron repletion assessments".

Step 2: Calculation and administration of the maximum individual iron dose(s):
Based on the iron need determined above the appropriate dose(s) of Iron (III) Isomaltoside 1000 solution for injection/infusion should be administered taking into consideration the following:
A single Iron (III) Isomaltoside 1000 solution for injection/infusion should not exceed 20 mg iron/kg body weight.

Step 3: Post-iron repletion assessments:
Re-assessment should be performed by the clinician based on the individual patient's condition. The Hb level should be re-assessed no earlier than 4 weeks post final Iron (III) Isomaltoside 1000 solution for injection/ infusion administration to allow adequate time for erythropoiesis and iron utilisation. In the event the patient requires further iron repletion, the iron need should be recalculated.

Children and adolescents:
Iron (III) Isomaltoside 1000 solution for injection/infusion is not recommended for use in children and adolescents < 18 years due to insufficient data on safety and efficacy.

Method of administration:
Iron (III) Isomaltoside 1000 solution for injection/infusion must be administered by the intravenous route either by injection or by infusion.

Intravenous bolus injection:
Iron (III) Isomaltoside 1000 solution for injection/infusion may be administered as an intravenous bolus injection up to 500 mg up to three times a week at an administration rate of up to 250 mg iron/minute. It may be administered undiluted or diluted in maximum of 20 ml sterile 0.9% sodium chloride.

Table 3: Administration rates for intravenous bolus injection

Volume of Iron(III) Isomaltoside 1000 Solution for Injection/Infusion	Equivalent Iron Dose	Administration Rate/Minimum Administration Time	Frequency
⩽5 ml	⩽500mg	250 mg iron/minute	1-3 times a week

Intravenous infusion:
The iron need required may be administered in a single Iron (III) Isomaltoside 1000 solution for injection/infusion up to 20 mg iron/kg body weight or as weekly infusions until the cumulative iron need has been administered.

If the iron need exceeds 20 mg iron/kg body weight, the dose must be split into two administrations with an interval of at least one week. It is recommended whenever possible to give 20 mg iron/kg body weight in the first administration. Dependent on clinical judgement the second administration could await follow-up laboratory tests.

Table 4: Administration rates for intravenous infusion

Iron dose	Minimum Administration Time
⩽1000 mg	More than 15 minutes
>1000 mg	30 minutes or more

Iron (III) Isomaltoside 1000 solution for injection/infusion should be infused undiluted or diluted in a sterile 0.9% sodium chloride solution. For stability reasons, Iron (III) Isomaltoside 1000 solution for injection/infusion should not be diluted to concentrations less than 1 mg iron/ml (not including the volume of the iron isomaltoside solution). Do not dilute in more than 500 ml. Please refer to section "storage & handling instructions".

Injection into dialyser:
Iron (III) Isomaltoside 1000 solution for injection/infusion may be administered during a haemodialysis session directly into the venous limb of the dialyser under the same procedures as outlined for intravenous bolus injection.

4.3 Contraindications
Iron (III) Isomaltoside 1000 solution for injection/infusion is contraindicated in the following situations:
- Hypersensitivity to the active substance, to Iron (III) Isomaltoside 1000 solution for injection/infusion or any of its excipients listed in section "composition"
- Non-iron deficiency anemia (e.g. haemolytic anemia)
- Iron overload or disturbances in the utilisation of iron (e.g. hemochromatosis, hemosiderosis)

4.4 Special warnings and precautions for use
Parenterally administered iron preparations can cause hypersensitivity reactions including serious and potentially fatal anaphylactic/anaphylactoid reactions. Hypersensitivity reactions have also been reported after previously uneventful doses of parenteral iron complexes. The risk is enhanced for patients with known allergies including drug allergies, previous severe hypersensitivity to other parenteral iron products, and patients with a history of severe asthma, eczema or other atopic allergies.

There is also an increased risk of hypersensitivity reactions to parenteral iron complexes in patients with immune or inflammatory conditions (e.g. systemic lupus erythematosus, rheumatoid arthritis). Iron (III) Isomaltoside 1000 solution for injection/infusion should only be administered when staff trained to evaluate and manage anaphylactic reactions is immediately available, in an environment where full resuscitation facilities can be assured. Each patient should be observed for adverse effects for at least 30 minutes following each injection of Iron (III) Isomaltoside 1000 solution for injection/infusion. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. Facilities for cardiorespiratory resuscitation and equipment for handling acute anaphylactic/anaphylactoid reactions should be available, including an injectable 1:1000 adrenaline solution. Additional treatment with antihistamines and/or corticosteroids should be given as appropriate.

In patients with liver dysfunction, parenteral iron should only be administered after careful benefit/risk assessment. Parenteral iron administration should be avoided in patients with hepatic dysfunction (alanine aminotransferase and/or aspartate aminotransferase > 3 times upper limit of normal) where iron overload is a precipitating factor, in particular Porphyria Cutanea Tarda (PCT). Careful monitoring of iron status is recommended to avoid iron overload. Parenteral iron should be used with caution in case of acute or chronic infection.

Iron (III) Isomaltoside 1000 solution for injection/infusion should not be used in a patient with ongoing bacteraemia.

Hypotensive episodes may occur if the intravenous injection is administered too rapidly.
Caution should be exercised to avoid paravenous leakage when administrating Iron (III) Isomaltoside 1000 solution for injection/infusion. Paravenous leakage of Iron (III) Isomaltoside 1000 solution for injection/infusion at the injection site may lead to irritation of the skin and potentially long-lasting brown discolouration at the site of injection. In case of paravenous leakage, the administration of Iron (III) Isomaltoside 1000 solution for injection/infusion must be stopped immediately. Distant skin discolouration has also been reported.
No studies on the effects on the ability to drive and use machines have been performed.

4.5 Drug Interactions
As with all parenteral iron preparations the absorption of oral iron is reduced when administered concomitantly.

Large doses of parenteral iron (5 ml or more) have been reported to give a brown colour to serum from a blood sample drawn four hours after administration.

Parenteral iron may cause falsely elevated values of serum bilirubin and falsely decreased values of serum calcium.

4.6 Use in the special population (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)
Pregnancy
There are no adequate and well-controlled trials of Iron (III) Isomaltoside 1000 solution for injection/infusion in pregnant women. A careful risk/benefit evaluation is therefore required before use during pregnancy and Iron (III) Isomaltoside 1000 solution for injection/infusion should not be used during pregnancy unless clearly necessary.
Iron deficiency anaemia occurring in the first trimester of pregnancy can in many cases be treated with oral iron. Treatment with Iron (III) Isomaltoside 1000 solution for injection/infusion should be confined to the second and third trimester if the benefit is judged to outweigh the potential risk for both the mother and the foetus.
Foetal bradycardia may occur following the administration of parenteral irons. It is usually transient and a consequence of a hypersensitivity reaction in the mother. The unborn baby should be carefully monitored during intravenous administration of parenteral irons to pregnant women.

Breast-feeding
A clinical study showed that the transfer of iron from Iron (III) Isomaltoside 1000 solution for injection/infusion to human milk was very low. At therapeutic doses of Iron (III) Isomaltoside 1000 solution for injection/infusion no effects on the breastfeeding newborns/infants are anticipated.

Fertility
There are no data on the effect of Iron (III) Isomaltoside 1000 solution for injection/infusion on human fertility. Fertility was unaffected following Iron (III) Isomaltoside 1000 solution for injection/infusion treatment in animal studies.

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects
The table presents the adverse drug reactions (ADRs) reported during Iron (III) Isomaltoside 1000 solution for injection/infusion treatment in clinical trials and in-market experience.

Acute severe hypersensitivity reactions may occur with parenteral iron preparations. They usually occur within the first few minutes of administration and are generally characterised by the sudden onset of respiratory difficulty and/or cardiovascular collapse; fatalities have been reported. Other less severe manifestations of immediate hypersensitivities, such as urticarial and itching may also occur. In pregnancy, associated foetal bradycardia may occur with parenteral iron preparations.

Fishbane reaction characterised by flushing in the face, acute chest and/or back pain and tightness sometimes with dyspnoea in association with IV iron treatment may occur (frequency uncommon). This may mimic the early symptoms of an anaphylactoid/anaphylactic reaction. The infusion should be stopped and the patient's vital signs should be assessed. These symptoms disappear shortly after the iron administration is stopped.

They typically do not reoccur if the administration is restarted at a lower infusion rate.

Distant skin discolouration has also been reported post marketing following IV iron administration.

Adverse drug reactions observed during clinical trials and post-marketing experience

System Organ Class	Common (⩾1/100 to <1/10)	Uncommon (⩾1/1000 to <1/100)	Rare (⩾1/10000 to <1/1000)
Immune system disorders		Hypersensitivity	Anaphylactoid/ anaphylactic reactions
Nervous system disorders		Headache, paraesthesia, dysgeusia, dizziness, fatigue	Dysphonia, seizure, tremor, altered mental status, blurred vision, loss of consciousness.
Cardiac disorders			Tachycardia, palpitations
Vascular disorders		Hypotension, hypertension	
Respiratory, thoracic and mediastinal disorders		Chest pain, dyspnoea, bronchospasm	
Gastrointestinal disorders	Nausea	Abdominal pain, vomiting, dyspepsia, constipation, diarrhoea	
Skin and subcutaneous tissue disorders	Rash	Pruritus, urticaria, flushing, sweating, dermatitis	
Metabolism and nutritional disorders		Hypophosphataemia	
Musculoskeletal and connective tissue disorders		Back pain, myalgia, arthralgia, muscle spasms	
General disorders and administration site conditions		Pyrexia, chills/shivering, infection, local phlebitic reaction, swelling, pain, skin exfoliation, injection site reactions*	Malaise, influenza like illness**
Investigations		Hepatic enzyme increased	

* Includes the following preferred terms, i.e. injection site erythema, swelling, burning, pain, bruising, discolouration, extravasation, irritation and reaction.
** Influenza-like illness whose onset may vary from a few hours to several days.

Description of selected adverse reactions
Delayed reactions may also occur with parenteral iron preparations and can be severe. They are characterised by arthralgia, myalgia and sometimes fever. The onset varies from several hours up to four days after administration. Symptoms usually last two to four days and settle spontaneously or following the use of simple analgesics.

4.9 Overdose
The Iron(III) Isomaltoside 1000 solution for injection/infusion has low toxicity. The preparation is well tolerated and has a minimal risk of accidental overdosing.
Overdose may lead to accumulation of iron in storage sites eventually leading to haemosiderosis. Monitoring of iron parameters such as serum ferritin may assist in recognising iron accumulation. Supportive measures such as chelating agents can be used.

5. PHARMACOLOGICAL PROPERTIES
Pharmaceutical Group: Iron trivalent parental preparation
ATC Code: B03AC

5.1 Mechanism of Action
Mechanism of action
Iron (III) Isomaltoside 1000 solution for injection/infusion solution for injection is a colloid with strongly bound iron in spheroidal iron-carbohydrate particles. The Iron (III) Isomaltoside 1000 solution for injection/infusion formulation contains iron in a complex that enables a controlled and slow release of bioavailable iron to iron-binding proteins with little risk of free iron.

5.2 Pharmacodynamic properties
The chelation of Iron (III) with carbohydrate confers to the particles a structure resembling ferritin that is suggested to protect against the toxicity of unbound inorganic Iron (III).

The iron is available in a non-ionic water-soluble form in an aqueous solution with pH between 5.0 and 7.0.

Evidence of a therapeutic response can be seen within a few days of administration of the Iron (III) Isomaltoside 1000 solution for injection/infusion as an increase in the reticulocyte count. Due to the slow release of bioavailable iron serum ferritin peaks within days after an intravenous dose of Iron (III) Isomaltoside 1000 solution for injection/infusion and slowly returns to baseline after weeks.

Although iron is the active compound in all parenteral iron preparations, Iron (III) Isomaltoside is different from other IV iron complexes such as iron dextran and ferric carboxymaltose. IV iron complexes are not clinically interchangeable.

5.3 Pharmacokinetic properties
The Iron (III) Isomaltoside 1000 solution for injection/infusion formulation contains iron in a strongly bound complex that enables a controlled and slow release of bioavailable iron to iron-binding proteins with little risk of free iron. After administration of a single dose of Iron (III) Isomaltoside 1000 solution for injection/infusion of 100 to 1000 mg of iron in pharmacokinetic studies, the iron injected or infused was cleared from the plasma with a half-life that ranged from 1 to 4 days. Renal elimination of iron was negligible.

Distribution
Following intravenous administration, Iron (III) Isomaltoside 1000 is rapidly taken up by the cells in the reticuloendothelial system (RES), particularly in the liver and spleen from where iron is slowly released.

Metabolism
Circulating iron is removed from the plasma by cells of the reticuloendothelial system which split the complex into its components of iron and isomaltoside 1000. The iron is immediately bound to the available protein moieties to form hemosiderin or ferritin, the physiological storage forms of iron, or to a lesser extent, to the transport molecule transferrin. This iron, which is subject to physiological control, replenishes haemoglobin and depleted iron stores.

Excretion
Iron is not easily eliminated from the body and accumulation can be toxic. Due to the size of the complex, Iron (III) Isomaltoside 1000 solution for injection/infusion is not eliminated via the kidneys. Small quantities of iron are eliminated in urine and faeces.

Isomaltoside 1000 is either metabolised or excreted.

6. NON CLINICAL PROPERTIES
6.1 Animal Toxicology or Pharmacology
Iron complexes have been reported to be teratogenic and embryocidal in non-anaemic pregnant animals at high single doses above 125 mg iron/kg body weight. The highest recommended dose in clinical use is 20 mg iron/kg body weight.

In a fertility study with Iron(III) Isomaltoside 1000 solution for injection/infusion in rats no effects on female fertility or male reproductive performance and spermatogenic parameters were found at the dose levels tested.

7. DESCRIPTION
Drug Substance: Iron (III) Isomaltoside 1000
Drug Product: A dark brown non-transparent Solution.

8. PHARMACEUTICAL PARTICULARS
8.1 Incompatibilities
This medicinal product must not be mixed with other medicinal products except following:
Iron (III) Isomaltoside 1000 solution for injection/infusion must only be mixed with sterile 0.9% sodium chloride. No other intravenous dilution solution should be used. No other therapeutic agents should be added.

8.2 Shelf life
See on pack.

Shelf life after first opening of the container (undiluted):
From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately.
If not used immediately, in-use storage time and condition are the responsibility of the user.

Shelf life after dilution with sterile 0.9% sodium chloride:
From a microbiological point of view, preparation for parenteral administration should be used immediately after dissolution with a sterile 0.9% sodium chloride solution.

8.3 Packaging information
1 vial of 5ml packed in a carton with leaflet.

8.4 Storage and handling instructions
Do not store above 30°C. Do not freeze.

For storage conditions of the reconstituted and diluted solution see section "Shelf Life".

Inspect vials visually for sediment and damage before use. Use only those containing sediment-free, homogeneous solutions.

Iron(III) Isomaltoside 1000 solution for injection/infusion is for single use only and any unused solution should be disposed of in accordance with local requirements.

9. PATIENT COUNSELING INFORMATION
Monitor carefully patients for signs and symptoms of hypersensitivity reaction during and following each administration of Iron (III) Isomaltoside 1000 solution for injection/infusion. Iron (III) Isomaltoside 1000 solution for injection/infusion should only be administered when staff trained to evaluate and manage anaphylactic reaction is immediately available, in an environment where full resuscitation facilities can be assured. The patient should be observed for adverse effects for at least 30 minutes following each Iron (III) Isomaltoside 1000 solution for injection/infusion injection.

Each IV iron administration is associated with a risk of a hypersensitivity reaction. Thus, to minimize risk the number of single IV iron administrations should be kept to a minimum.

Extensively, patients should be counselled on the appropriate use of Iron (III) Isomaltoside with close monitoring of the Dosages and side effects.

10. DET

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