PROFESSIONAL INFORMATION

SCHEDULING STATUS S3

1 NAME OF THE MEDICINE

Fortihem™ 20 mg/mL (solution for injection/concentrate for solution for infusion)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:

Each ampoule contains 100 mg iron as iron(III)-hydroxide sucrose complex per 5 mL solution; 20 mg iron per 1 mL.

Contains sugar.

Excipients:

For excipients, please see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/concentrate for solution for infusion.

FORTIHEM is a dark brown, colloidal, aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Severe iron deficiency in adult patients not tolerating or responding to oral iron. FORTIHEM is recommended for use only where the indication is definite and confirmed by appropriate investigations.

4.2 Posology and method of administration

Calculation of dosage:

Adults and the elderly:

The total cumulative dose of FORTIHEM is determined by the haemoglobin level and body weight.

The dose and dosage schedule for FORTIHEM must be individually estimated for each patient based on a calculation of the total iron deficit.

Total iron deficit [mg] = body weight [kg] x (target Hb–actual Hb)

[g/dl] x 2,4* + depot iron [mg]

Below 35 kg weight: target Hb = 13 g/dl depot iron = 15 mg/kg body weight

35 kg body weight and above: target Hb = 15 g/dl depot iron = 500 mg

* Factor 2,4 = 0,0034 x 0,07 x 1000 x 10

Where 0,0034 = Iron content of haemoglobin = 0,34 %

0,07 = Blood volume = 7 % of body weight

1000 = Factor = conversion from g to mg

10 = Factor = conversion from g/dl to g/L.

Total number of FORTIHEM ampoules to be administered				
Body weight (kg)	**Haemoglobin 6,0 g/dl**	**Haemoglobin 7,5 g/dl**	**Haemoglobin 9,0 g/dl**	**Haemoglobin 10,5 g/dl**
30	9,5	8,5	7,5	6,5
35	12,5	11,5	10,0	9,0
40	13,5	12,0	11,0	9,5
45	15,0	13,0	11,5	10,0
50	16,0	14,0	12,0	10,5
55	17,0	15,0	13,0	11,0
60	18,0	16,0	13,5	11,5

65	19,0	16,5	14,5	12,0
70	20,0	17,5	15,0	12,5
75	21,0	18,5	16,0	13,0
80	22,5	19,5	16,5	13,5
85	23,5	20,5	17,0	14,0
90	24,5	21,5	18,0	14,5

Total ampoules of FORTIHEM to be administered = $\frac{\text{Total iron deficit (mg)}}{100 \text{ mg}}$

The total single dose must not exceed 200 mg of iron given not more than three times per week. If the total necessary dose exceeds the maximum allowed single dose, then the administration has to be split.

Children:

The use of FORTIHEM has not been adequately studied in children and therefore FORTIHEM is not recommended for use in children.

Method of administration:

FORTIHEM must be administered by a slow intravenous injection, by an intravenous drip infusion or, in patients receiving haemodialysis, into the venous limb of the dialyser (see section 4.4).
FORTIHEM is a strongly alkaline solution and must never be administered by the subcutaneous or intramuscular route. Paravenous leakage must be avoided because leakage of FORTIHEM at the injection site may lead to pain, inflammation, tissue necrosis, and brown discolouration of the skin.

FORTIHEM is not suitable for intramuscular use nor for TDI (Total Dose Infusion).
TEST DOSE

Before administration of the first therapeutic dose of FORTIHEM in a new patient, a test dose of 1 mL to 2,5 mL FORTIHEM (20 mg to 50 mg iron) should be given by the chosen method of administration (see below). If no adverse reaction occurs within a waiting period of at least 15 minutes after administration, the remaining portion of the initial dose may be given.

Infusion:

The content of one ampoule has to be diluted exclusively in 100 mL of sterile 0,9 % *m/v* sodium chloride solution, immediately prior to infusion (i.e. 2 ampoules in 200 mL sterile 0,9 % *m/v* NaCl).
The first 25 mg of iron (i.e. 25 mL of solution) should be infused as a test dose over a period of 15 minutes (see above TEST DOSE). If no adverse reaction occurs during this time then the remaining portion of the infusion should be given as follows:

- 100 mg iron (5 mL FORTIHEM) in at least 15 minutes
- 200 mg iron (10 mL FORTIHEM) in at least 30 minutes

Intravenous injection:

As an intravenous injection FORTIHEM must be administered slowly at a rate of 1 mL undiluted solution per minute (i.e. 5 minutes per ampoule), not exceeding 2 ampoules FORTIHEM (200 mg iron) per injection. Before administering a slow intravenous injection, a test dose of 1 mL (20 mg of iron) should be injected slowly over a period of 1 to 2 minutes. If no adverse event occurs within 15 minutes of completing the test dose, the remaining portion of the injection may be given.

Injection into dialyser:

FORTIHEM may be administered during a haemodialysis session directly into the venous limb of the dialyser under the same procedures as those outlined for intravenous injection.

4.3 Contraindications

The use of FORTIHEM is contraindicated in the following conditions:

- Hypersensitivity to the active substance or any of the excipients listed in section 6.1.
- Iron overload or disturbances in utilisation of iron (e.g., haemochromatosis, haemosiderosis).
- Anaemia not caused by iron deficiency (e.g., haemolytic anaemias).
- Known hypersensitivity to iron mono-, disaccharide complexes.
- Clinical or biochemical evidence of liver damage.
- Infectious hepatitis.
- Acute or chronic infection.
- A history of asthma, eczema, other allergic disorders or anaphylactic reactions.
- The safety in lactation and children has not been established.
- Pregnancy first semester.

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 including iron sucrose. There have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction, see section 4.8). In several studies performed in patients who had a history of a hypersensitivity reaction to iron dextran or ferric gluconate, iron sucrose was shown to be well tolerated. For known serious hypersensitivity to other parenteral iron products see section 4.3.

The risk of hypersensitivity reactions is enhanced for patients with known allergies including medicine allergies, including patients with a history of severe asthma, eczema or other atopic allergy.

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 sucrose, as in FORTIHEM, 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

iron sucrose, as in FORTIHEM, injection. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. Facilities for cardio respiratory 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.

FORTIHEM is contraindicated in patients with clinical or biochemical evidence of liver damage and in patients with hepatic dysfunction where iron overload is a precipitating factor, in particular Porphyria Cutanea Tarda (PCT) (see section 4.3). Careful monitoring of iron status is recommended to avoid iron overload.

FORTIHEM is also contraindicated in the case of acute or chronic infection (see section 4.3). It is recommended that the administration of FORTIHEM is stopped in patients with bacteraemia.

Paravenous leakage must be avoided because leakage of FORTIHEM at the injection site can lead to pain, inflammation and brown discoloration of the skin.

Hypotensive episodes may occur if the injection is administered too rapidly.

Patients with low iron binding capacity and/or folic acid deficiency are particularly at risk of an allergic or anaphylactic reaction. In cases of inadvertent paravenous leakage, and while the needle is still inserted, rinse with a small amount of 0,9 % sodium chloride solution.

FORTIHEM should not be administered in combination with oral iron preparations. FORTIHEM must not be mixed with other medicines for simultaneous administration. A sterile 0,9 % *m/v* sodium chloride solution is the only recommended diluent for an infusion.

Ampoules should be visually inspected for damage before use and only those with a sediment-free solution may be used. From a microbiological point of view, the product should be used immediately after first opening the container or after dilution with sterile 0,9 % *m/v* sodium chloride. Residual solvents must be discarded once the ampoule has been opened.

Porphyria: Safety has not been established.

4.5 Interaction with other medicines and other forms of interaction

As with all parenteral iron preparations, FORTIHEM should not be administered concomitantly with oral iron preparations since the absorption of oral iron is reduced. Therefore, oral iron therapy should be started at least 5 days after the last injection of FORTIHEM.
FORTIHEM must not be mixed with other medicines for simultaneous administration.

4.6 Fertility, pregnancy and lactation

Pregnancy:

The use of FORTIHEM in pregnant women in the first trimester is contraindicated (see section 4.3). Data (303 pregnancy outcomes) from the use of iron sucrose, as in FORTIHEM, in pregnant women in the second and third trimester showed no safety concerns for the mother or newborn.
FORTIHEM 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 FORTIHEM should be confined to second and third trimester and only be used in pregnant women with severe iron deficiency anaemia, where there is inability to absorb or tolerate adequate amounts of oral iron.
Foetal bradycardia may occur following 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.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Breastfeeding:

Safety during lactation has not been established.
There is limited information on the excretion of iron in human milk following administration of intravenous iron sucrose. In one clinical study, 10 healthy breast-feeding mothers with iron deficiency received 100 mg iron in the form of iron sucrose. Four days after treatment, the iron content of the breast milk had not increased and there was no difference from the control group (n=5). It cannot be excluded that newborns/infants may be exposed to iron derived from FORTIHEM via the mother's milk, therefore the risk/benefit should be assessed.

Preclinical data do not indicate direct or indirect harmful effects to the nursing child. In lactating rats treated with ^{59}Fe-labelled iron sucrose, low secretion of iron into the milk and transfer of iron into the offspring was observed. Non-metabolised iron sucrose is unlikely to pass into the mother's milk.

Fertility:

No effects of iron sucrose treatment were observed on fertility and mating performance in rats.

4.7 Effects on ability to drive and use machines

In the case of symptoms of dizziness, confusion or light-headedness following the administration of FORTIHEM, patients should not drive or use machinery until the symptoms have ceased.

4.8 Undesirable effects

The most commonly reported adverse drug reaction in clinical trials with iron sucrose, as in FORTIHEM was dysgeusia, which occurred with a rate of 4,5 events per 100 subjects. The most important serious adverse drug reactions associated with iron sucrose, as in FORTIHEM, are hypersensitivity reactions, which occurred with a rate of 0,25 events per 100 subjects in clinical trials. Anaphylactoid/anaphylactic reactions were reported only in the post-marketing setting (estimated as rare); fatalities have been reported. See section 4.4.

The adverse drug reactions reported after the administration of iron sucrose, as in FORTIHEM are presented below.

Immune system disorders:

Less frequent: Hypersensitivity

Frequency not known: Anaphylactoid/anaphylactic reactions, angioedema

Nervous system disorders:

Frequent: Dysgeusia

Less frequent: Headache, dizziness, paraesthesia, hypoaesthesia, syncope, somnolence

Frequency not known: Depressed level of consciousness, confusional state, loss of consciousness, anxiety, tremor

Cardiac disorders:

Frequent: Palpitations

Less frequent: Bradycardia, tachycardia, Kounis syndrome

Vascular disorders:

Frequent: Hypotension, hypertension

Less frequent: Flushing, phlebitis

Frequency not known: Circulatory collapse, thrombophlebitis

Respiratory thoracic and mediastinal disorders:

Less frequent: Dyspnoea

Frequency not known: Bronchospasm

Gastrointestinal disorders:

Frequent: Nausea

Less frequent: Vomiting, abdominal pain, diarrhoea, constipation

Skin and subcutaneous tissue disorders:

Less frequent: Pruritis, rash

Frequency not known: Urticaria, erythema

Musculoskeletal and connective tissue disorders:

Less frequent: Muscle spasm, myalgia, arthralgia, pain in extremity, back pain

Renal and urinary disorders:

Less frequent: Chromaturia

General disorders and administration site conditions:

Frequent: Injection/infusion site reaction[2]

Less frequent: Chills, asthenia, fatigue, oedema peripheral, pain, chest pain, hyperhidrosis, pyrexia

Frequency not known: Cold sweat, malaise, pallor, influenza like illness[3]

Investigations:

Less frequent: Alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, serum ferritin increased, blood lactate dehydrogenase increased

[2] The most frequently reported area: injection/infusion site pain, extravasation, irritation, reaction, discolouration, haematoma, pruritis.

[3] Onset may vary from a few hours to several days.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8. Suspected adverse reactions can also be reported directly to the HCR via pvi1j.solutions.iqvia.com or adverse.event.sac@sandoz.com.

4.9 Overdose

Overdose can cause iron overload which may manifest itself as haemosiderosis. Overdose should be treated, as deemed necessary by the treating medical practitioner, with an iron chelating agent or according to standard medical practice.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-anaemic preparation, iron, parenteral preparation.

A 8.3 – Erythropoietics (haematinics)

ATC code: B03AC

Mechanism of action:

Iron sucrose, the active ingredient of FORTIHEM, is composed of a polynuclear iron(III)-hydroxide core surrounded by a large number of non-covalently bound sucrose molecules. The complex has a weight average molecular weight (Mw) of approximately 43 kDa. The polynuclear iron core has a structure similar to that of the core of the physiological iron storage protein ferritin. The complex is designed to provide, in a controlled manner, utilisable iron for the iron transport and storage proteins in the body (i.e., transferrin and ferritin, respectively).

Following intravenous administration, the polynuclear iron core from the complex is taken up predominantly by the reticuloendothelial system in the liver, spleen, and bone marrow. In a second step, the iron is used for the synthesis of Hb, myoglobin and other iron-containing enzymes, or stored primarily in the liver in the form of ferritin.

5.2 Pharmacokinetic properties

Distribution:

The volume of distribution at steady state is about 8 litres, which indicates a low iron distribution in the body fluid. Due to the lower stability of Iron(III)-Hydroxide Sucrose Complex in comparison to transferrin, a competitive exchange of iron to transferrin was observed. This results in an iron transport of approximately 31 mg iron/24 hours.

The ferrokinetics of iron sucrose labelled with ^{52}Fe and ^{59}Fe were assessed in 6 patients with anaemia and chronic renal failure. In the first 6–8 hours, ^{52}Fe was taken up by the liver, spleen and bone marrow.

The radioactive uptake by the macrophage-rich spleen is considered to be representative of the reticuloendothelial iron uptake.
Following intravenous injection of a single 100 mg iron dose of iron sucrose in healthy volunteers, maximum total serum iron concentrations were attained 10 minutes after injection and had an average concentration of 538 µmol/l. The volume of distribution of the central compartment corresponded well to the volume of plasma (approximately 3 litres).

Biotransformation:

Upon injection, sucrose largely dissociates and the polynuclear iron core is mainly taken up by the reticuloendothelial system of the liver, spleen, and bone marrow. At 4 weeks after administration, red cell iron utilization ranged from 59 to 97 %.

Elimination:

The iron injected is quickly cleared from the plasma, the terminal half-life is approximately 6 hours.
The iron sucrose complex has a weight average molecular weight (Mw) of approximately 43 kDa, which is sufficiently large to prevent renal elimination. Renal elimination of iron, occurring in the first 4 hours after injection of a FORTIHEM dose of 100 mg iron, corresponded to less than 5 % of the dose. After 24 hours, the total serum iron concentration was reduced to the pre-dose level. Renal elimination of sucrose was about 75 % of the administered dose.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injection, sodium hydroxide 5N (pH adjuster).

6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in section 6.6. There is the potential for precipitation and/or interaction if mixed with other solutions or medicines. The compatibility with containers other than glass, polyethylene and PVC is not known.

6.3 Shelf life

Shelf life of the product as packaged for sale:

36 months.

Shelf life after first opening of the container:

From a microbiological point of view, the product should be used immediately.

Shelf life after dilution with sterile 0,9 % *m/v* sodium chloride (NaCl) solution:

From a microbiological point of view, the product should be used immediately after dilution with sterile 0,9 % *m/v* sodium chloride solution.

6.4 Special precautions for storage

Store at or below 25 °C. Do not freeze. Store in the original package.

For storage conditions after dilution or first opening of the medicine, see section 6.3.

6.5 Nature and contents of container

Immediate container:

FORTIHEM, solution for injection/concentrate for solution for infusion is filled in clear hydrolytic glass (Ph. Eur., Type I) ampoules.

Each ampoule contains 5 mL of solution, according to the proposed packaging size of the medicine.

Secondary container:

A carton box containing a specific plastic holding case, which there in after holds 5 ampoules along with the patient information leaflet.

6.6 Special precautions for disposal and other handling

Ampoules or vials should be visually inspected for sediment and damage before use. Use only those containing a sediment free and homogenous solution.

FORTIHEM must not be mixed with other medicines except sterile 0,9 % *m/v* sodium chloride solution for dilution. For instructions on dilution of the product before administration, see section 4.2.

The diluted solution must appear as brown and clear.

Each ampoule or vial of FORTIHEM is intended for single use only.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Magwa Crescent West

Waterfall City

Jukskei View

Midrand

2090

8 REGISTRATION NUMBER

50/8.3/1051

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22 February 2022

10 DATE OF REVISION OF THE TEXT

28 May 2024

[1]Company Reg. No.: 1990/001979/07