PACKAGE INSERT FOR Rautevene solution for injection / concentrate for solution for infusion

Scheduling Status: **S3**

Proprietary name and dosage form:

Rautevene solution for injection / concentrate for solution for infusion

Composition:

Each 5 ml ampoule contains 100 mg iron in the form of iron (III)-hydroxide sucrose complex, 20 mg iron per ml.

Excipient: Water for injection.

Osmolarity: Approximately 1250 mOsmol/l.

Contains no preservatives.

Contains sugar (approximately 30 % sucrose).

Pharmacological classification:

A 8.3 Erythropoietics (haematinics).

Pharmacological action:

Pharmacodynamic properties:

The polynuclear iron (III)-hydroxide cores are superficially surrounded by a large number of non-covalently bound sucrose molecules resulting in a complex with a molecular weight of approximately 43 kD.

This is sufficiently large to prevent renal elimination.

The resulting complex is stable and does not release ionic iron under physiologic conditions.

The iron in the polynuclear cores is bound in a similar structure to naturally occurring ferritin.

Pharmacokinetic properties:

The pharmacokinetics of the iron (III)-hydroxide sucrose complex was studied in healthy volunteers following the administration of a single intravenous injection of 100 mg iron. Peak serum iron concentrations, averaging

538 µmol/l were reached 10 minutes after injection.

The volume of distribution of the central compartment corresponds to the serum volume (approximately 3 litres).

The iron injected is quickly cleared from the serum. The distribution half-life is approximately 6 hours.

The volume of distribution at steady state is about 8 litres. This indicates a low iron distribution in the body fluid.

As a result of the lower stability of the iron (III) hydroxide-sucrose complex compared with transferrin, competitive exchange of iron to transferrin was observed, resulting in iron transport of approximately 31 mg Fe (III) per 24 hours.

Renal elimination of iron, occurring in the first 4 hours after injection, corresponds to less than 5 % of the total body clearance (approximately 20 ml/minute).

After 24 hours the serum iron levels decreased to the pre-dose iron concentration and, approximately 75 % of the sucrose dose was excreted.

Indications:

Severe iron deficiency in adult patients not tolerating or responding to oral iron.

RAUTEVENE is recommended for use only where the indication is definite and confirmed by appropriate investigations.

Contraindications:

The use of RAUTEVENE is contraindicated in the following conditions:

- Anaemias not caused by iron deficiency (e.g. haemolytic anaemias).
- Known hypersensitivity to iron monosaccharide or disaccharide complexes or any of the ingredients of RAUTEVENE.
- Iron storage disease (iron overload e.g. haemochromatosis, haemosiderosis).
- Disturbances in utilisation of iron (e.g. thalassaemia, sideroachrestic anaemias).
- 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 children has not been established.
- The safety in lactation has not been established.
- First trimester of pregnancy.

Warnings and special precautions:

RAUTEVENE contains sucrose.

Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose mal-absorption or sucrase-isomaltase insufficiency should not take RAUTEVENE.

The sucrose contained in RAUTEVENE may have an effect on the glycaemic control of patients with diabetes mellitus.

RAUTEVENE has a pH of 11 and must therefore be given **strictly by the intravenous route**.

The maximum daily dose of 200 mg should not be exceeded.

RAUTEVENE should only be used for the approved indications.

RAUTEVENE should only be administered if iron deficiency has been diagnostically established and confirmed by suitable laboratory tests (e.g. blood ferritin levels, haemoglobin, haemocrit or red blood cell count) and, calculated from the latter mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH) and mean corpuscular haemoglobin concentration (MCHC).

RAUTEVENE may cause hypersensitivity reactions including serious and potentially fatal anaphylactic/anaphylactoid reactions. Hypersensitivity reactions have also been reported after previously uneventful exposure to parenteral iron complexes.

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

There is an increased risk of hypersensitivity reactions to parenteral iron complexes in patients with immune or inflammatory conditions (e.g. systemic lupus erythematosus, rheumatoid arthritis).

RAUTEVENE should only be administered in an environment where full resuscitation can be assured and when staff trained to evaluate and manage anaphylactic reactions is immediately available. Each patient should be observed for adverse effects for at least 30 minutes following each RAUTEVENE 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 1:1 000 epinephrine (adrenaline) solution. Additional treatment with antihistamines and/or corticosteroids should be given as appropriate.

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

Patients with low binding capacity and/or folic acid deficiency are at increased risk of allergic or anaphylactic reactions.

Paravenous leakage must be avoided. In cases of inadvertent paravenous leakage, and while the needle is still inserted, rinse with a small amount of 0,9 % *m/v* sodium chloride solution.

Porphyria: Safety has not been established.

Effects on ability to drive and use machines:

After being given RAUTEVENE, the patient may feel dizzy, confused or lightheaded.

If this happens, the patient should be advised not to drive or use any machinery.

Interactions:

RAUTEVENE should not be administered concomitantly with oral iron preparations, since the absorption of oral preparations is reduced.

Pregnancy and lactation:

RAUTEVENE should not be used in the first trimester of pregnancy (see **Contraindications**).

In the second and third trimester RAUTEVENE should only be used after careful benefit-risk assessment and only in cases of severe iron deficiency anaemia where there is an inability to absorb or tolerate adequate

amounts of oral iron.

Safety during lactation has not been established.

Mothers on RAUTEVENE should not breastfeed their infants.

Dosage and directions for Use:

RAUTEVENE should not be administered in combination with oral iron preparations.

RAUTEVENE must not be mixed with other medicines for simultaneous administration.

The only recommended diluent for an infusion is a 0,9 % *m/v* sodium chloride solution.

RAUTEVENE is for single use only – Please discard any unused portion.

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.

Administration:

RAUTEVENE must be administered by slow intravenous injection, by an intravenous drip infusion or, in patients receiving haemodialysis, into the venous limb of the dialyser (see **Warnings and special precautions**).

RAUTEVENE is a strongly alkaline solution and must never be administered by the subcutaneous or intramuscular route.

Paravenous leakage must be avoided because leakage of RAUTEVENE at the injection site may lead to pain, inflammation, tissue necrosis, and brown discolouration of the skin.

RAUTEVENE is not suitable for intramuscular use or for TDI (Total Dose Infusion).

TEST DOSE:

Before administration of the first therapeutic dose of RAUTEVENE in all patients, a test dose of 1 to 2,5 ml RAUTEVENE (20 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.

Monitor patients carefully for signs and symptoms of hypersensitivity reactions during and following each administration of RAUTEVENE.

RAUTEVENE should only be administered in an environment where full resuscitation facilities can be assured and when staff trained to evaluate and manage anaphylactic reactions is immediately available. The patient should be observed for adverse effects for at least 30 minutes following each RAUTEVENE injection (see **Warnings and special precautions**).

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.

Dilution must take place immediately prior to infusion and the solution should be administered as follows:

- 100 mg iron (5 ml RAUTEVENE) in at least 15 minutes
- 200 mg iron (10 ml RAUTEVENE) in at least 30 minutes

Intravenous injection:

As an intravenous injection RAUTEVENE must be administered slowly at a rate of 1 ml undiluted solution per minute (i.e. 5 minutes per ampoule), not exceeding 2 ampoules RAUTEVENE (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 within 15 minutes of completing the test dose no adverse event occurs, the remaining portion of the injection may be given.

Injection into dialyser:

RAUTEVENE 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.

Dosage:

Calculation of dosage:

Adults and the elderly:

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

The dose and dosage schedule for RAUTEVENE 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 resp. depot iron **=** 15 mg/kg body weight

Above 35 kg body weight: Target Hb **=** 15 g/dl resp. 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 RAUTEVENE AMPOULES TO BE ADMINISTERED.

Body weight kg	Haemoglobin 6 g/dl	Haemoglobin 7,5 g/dl	Haemoglobin 9 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

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

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:

RAUTEVENE is not recommended for use in children since the use of RAUTEVENE in children has not been adequately studied.

Side effects:

Cardiac disorders:

Less frequent: Tachycardia and palpitations.

Vascular disorders:

Less frequent: Hypotension and collapse.

Gastro-intestinal disorders:

Less frequent: Nausea, vomiting, abdominal pain, diarrhoea.

General disorders and administrative site conditions:

Less frequent: Fever, shivering, flushing, chest pain and tightness.

Injection site disorders such as superficial phlebitis, burning, swelling.

Fatigue, asthenia, malaise.

Hyperhidrosis.

Immune system disorders:

Less frequent: Anaphylactic and anaphylactoid reactions (involving arthralgia), peripheral oedema, angioedema.

Nervous system disorders:

Frequent: Transient taste perversions (in particular metallic taste).

Less frequent: Reduced level of consciousness, lightheaded feeling, confusion, headache, dizziness, paraesthesia.

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Muscle cramps, myalgia, swelling of joints, back pain.

Respiratory, thoracic and mediastinal disorders:

Less frequent: Bronchospasm, dyspnoea.

Skin and subcutaneous tissue disorders:

Less frequent: Pruritus, urticaria, rash, exanthema, erythema.

Known symptoms of overdosage and particulars of its treatment:

Overdosage can cause acute iron overloading which may manifest itself as haemosiderosis.

Particular caution should be exercised to avoid iron overload where anaemia, non-response to treatment, has been incorrectly diagnosed as iron deficiency anaemia (see **Contraindications**).

Overdosage should be treated, if required, with an iron chelating agent.

Identification:

Dark brown colloidal solution in 5 ml clear glass ampoules.

Presentation:

5 ml clear glass ampoules in packs of 5 ampoules.

Storage instructions:

Store at or below 25 °C, in the original carton until required for use.

Do not refrigerate or freeze.

Solution for injection*:*

Once the ampoules have been opened they should be used immediately.

Concentrate for solution for infusion*:*

Once prepared (diluted), the solution for infusion should be used immediately.

KEEP OUT OF REACH OF CHILDREN.

Registration number: 46/8.3/0849

Name and business address of the holder of the certificate of registration:

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