

SCHEDULING STATUS**S3****1 NAME OF THE MEDICINE**

EQUIFER solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml contains iron (III)-hydroxide sucrose equivalent to 20 mg iron and each 5 ml ampoule contains 100 mg iron in the form of iron (III)-hydroxide sucrose complex. Contains no preservatives.

The osmolality of the solution is between 1150 - 1350 mOsmol/l.

Contains sucrose 27-33 % w/v.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.

Dark brown solution free of any sediment.

4 CLINICAL PARTICULARS**4.1 Therapeutic indications**

EQUIFER is indicated for severe iron deficiency in adult patients not tolerating or responding to oral iron.

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

4.2 Posology and method of administration**Posology*****Calculation of dosage******Adults and the elderly:***

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

dose and dosage schedule for EQUIFER 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

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

* Factor 2,4 = $0,0034 \times 0,07 \times 1000 \times 10$

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 EQUIFER 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

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

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.

Paediatric population

The use of EQUIFER has not been adequately studied in children and therefore EQUIFER is not recommended for use in children (see section 4.3).

Method of administration

EQUIFER must only be administered by the intravenous route. This may be by a slow intravenous injection or by an intravenous drip infusion or into the venous limb of the dialyser, the latter being only applicable to patients receiving haemodialysis (see section 4.4).

Administration by intravenous drip infusion is the preferred route of administration as this may help to reduce the risk of hypotensive episodes and paravenous leakage. Before administering the first dose to a new patient, a test dose of EQUIFER should be given.

Facilities for cardio-pulmonary resuscitation must be available when administering EQUIFER because allergic or anaphylactic reactions and hypotensive episodes may occur.

EQUIFER is a strongly alkaline solution and must never be administered by the subcutaneous or intramuscular route. Paravenous leakage must be avoided because leakage of EQUIFER at the injection site may lead to pain, inflammation, tissue necrosis, sterile abscess and brown discolouration of the skin (see section 4.4 and 4.8).

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

TEST DOSE

Before administration of the first therapeutic dose of EQUIFER in a new patient, a test dose of 1 ml to 2,5 ml EQUIFER (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

EQUIFER should preferably be administered by drip infusion (in order to reduce the risk of hypotensive episodes and paravenous leakage). The content of one ampoule has to be diluted exclusively in 100 ml of 0,9 % w/v sodium chloride solution, immediately prior to infusion (i.e., 2 ampoules in 200 ml 0,9 % w/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 as follows:

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

Intravenous injection

As an intravenous injection EQUIFER must be administered slowly at a rate of 1 ml undiluted solution per minute (i.e., 5 minutes per ampoule), not exceeding 2 ampoules EQUIFER (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. After an intravenous injection, extend and elevate the patient's arm and apply pressure to the injection site for at least 5 minutes to reduce the risk of paravenous leakage.

Injection into dialyser

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

4.3 Contraindications

- Known hypersensitivity to iron mono- or di-saccharide complexes or other ingredients of EQUIFER.
- Anaemia not caused by iron deficiency (e.g., haemolytic anaemia).
- Iron overload or disturbances in utilisation of iron (e.g., haemosiderosis or haemochromatosis).
- Clinical or biochemical evidence of liver damage.
- Infectious hepatitis.
- Acute or chronic infection.
- Patients with a history of asthma, eczema, other allergic disorders or anaphylactic reactions.
- First trimester of pregnancy.
- The safety in lactation has not been established.
- The safety in children has not been established.

4.4 Special warnings and precautions for use

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

EQUIFER has a pH of 11 and must therefore be given **strictly by the intravenous route** (see section 4.2), and the maximum daily dose of 200 mg should not be exceeded.

EQUIFER should only be used for the approved indications.

Iron preparations administered parentally, can cause severe allergic or anaphylactic reactions. For this reason EQUIFER should only be used in facilities where cardio-pulmonary resuscitation can be performed. In the event of a serious anaphylactic or allergic reaction, administration of EQUIFER

must be stopped, intramuscular or intravenous epinephrine (adrenaline) should be administered immediately and other supportive measures initiated in line with the established cardio-pulmonary resuscitation procedures. 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.

In the event of mild allergic reactions, the administration of EQUIFER should be stopped and treatment with antihistamines should be started.

Patients with rheumatoid arthritis may develop worsening of symptoms when given EQUIFER. Patients with other inflammatory disorders may be at increased risk of delayed reactions.

Rapid administration of EQUIFER injection may result in hypotensive episodes.

Safety in porphyria has not been established.

Patients with low iron binding capacity and/or folic acid deficiency are particularly at risk of an allergic or anaphylactoid reaction. Anaphylactoid reactions are the most serious side effects.

A TEST DOSE (see section 4.2) is recommended and facilities for resuscitation should be available. Mild allergic reactions should be managed by stopping the administration of EQUIFER and administering antihistamines.

In the case of an anaphylactic reaction, epinephrine (adrenaline) should be administered immediately.

In the case of inadvertent paravenous leakage, while the needle is still inserted rinse with a small amount

of 0,9 % sodium chloride solution.

Symptomatic hypophosphataemia leading to osteomalacia and fractures requiring clinical intervention including surgery has been reported in the post-marketing setting.

- Patients should be advised to seek medical advice if they experience worsening fatigue with myalgias or bone pain.
- Serum phosphate should be monitored in patients who receive multiple administrations at higher doses or long-term treatment, and those with existing risk factors such as vitamin D deficiency, calcium and phosphate malabsorption, secondary hyperparathyroidism, hereditary hemorrhagic telangiectasia, inflammatory bowel disease, and osteoporosis.
- In case of persisting hypophosphataemia, treatment should be re-evaluated.

4.5 Interaction with other medicines and other forms of interaction

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

The response to EQUIFER may be delayed in patient receiving systemic chloramphenicol.

Enalapril may possibly potentiate the adverse systemic reactions seen with EQUIFER injection.

4.6 Fertility, pregnancy and lactation

Pregnancy

EQUIFER is recommended for use in the second and third trimester and not for use during the first trimester of pregnancy (see section 4.3).

EQUIFER should only be used in pregnant women with severe iron deficiency anaemia; where there is inability to absorb or tolerate adequate amounts of oral iron.

Breastfeeding

Safety during lactation has not been established.

4.7 Effects on ability to drive and use machines

After being given EQUIFER, the patient may feel dizzy, confused or lightheaded. If this happens, the patient should be advised not to drive or use any tools or machines.

4.8 Undesirable effects

Immune system disorders

Less frequent: Anaphylactic and anaphylactoid reactions (involving arthralgia); angioedema.

Nervous system disorders

Frequent: Headache, dizziness.

Less frequent: Paraesthesia, reduced level of consciousness, lightheaded feeling and confusion.

Cardiac disorders

Less frequent: Tachycardia, palpitations; chest pain or tightness.

Frequency unknown: Myocardial infarction, bradycardia and dysrhythmias.

Vascular disorders

Less frequent: Hypotension, collapse, oedema of the extremities.

Frequency unknown: Hypertension.

Respiratory, thoracic and mediastinal disorders

Less frequent: Bronchospasm, dyspnoea.

Gastrointestinal disorders

Frequent: Metallic taste or taste disturbance.

Less frequent: Gastrointestinal disturbance (nausea and vomiting), abdominal pain, diarrhoea.

Skin and subcutaneous tissue disorders

Frequent: Brown discolouration of skin.

Less frequent: Urticaria, pruritus, erythema, exanthema.

Frequency unknown: Rash, purpura.

Musculoskeletal and connective tissue disorders

Less frequent: Muscular pain, muscle cramps, myalgia.

Frequency unknown: Backache, arthralgia, swelling of joints, hypophosphataemic osteomalacia.

Renal and urinary disorders

Frequency unknown: Haematuria.

General disorders and administrative site conditions

Less frequent: Shivering, fever, flushing, fatigue, asthenia, malaise and hyperhidrosis. Injection site disorders such as burning, swelling, superficial phlebitis and venous spasm.

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>

4.9 Overdose

Overdose can cause acute iron overloading which may manifest as haemosiderosis.

Particular caution should be exercised to avoid iron overload where anaemia, unresponsive to treatment, has been incorrectly diagnosed as iron deficiency anaemia.

An iron overdosage can only be treated with an iron chelating agent, desferrioxamine, normally in combination with ascorbic acid. Desferrioxamine infusion should be given strictly according to the recommendations on the package insert.

With chronic repeated administration of iron at high dose, the excess iron will accumulate in the liver and induce an inflammatory process, which may lead to fibrosis.

Patients must be monitored for a minimum of 24 hours after becoming asymptomatic. Delayed effects may include shock and severe gastrointestinal bleeding. Residual damage may be ruled out with liver and upper gastrointestinal studies.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 8.3 – Erythropoietics (haematinics).

Pharmacotherapeutic group: Anti-anaemic preparation, iron, parenteral preparation, ATC code: B03AC.

EQUIFER is an iron (III)-hydroxide sucrose complex, which is considered to be polynuclear. A large number of non-covalently bound sucrose molecules superficially surround the polynuclear iron (III)-hydroxide cores, resulting in an overall complex molecular mass M_w of approximately 43kD, which is large enough to prevent renal elimination. The resulting complex does not release ionic iron under physiological conditions and is considered stable. The iron in the polynuclear cores is bound in a similar structure as in the case of physiologically occurring ferritin.

5.2 Pharmacokinetic properties

A maximum mean iron level of 538 $\mu\text{mol/l}$ is reached after 10 minutes after a single IV administration of 100 mg iron (III)-hydroxide sucrose complex to healthy subjects. The volume of distribution of the central compartment corresponds to the volume of plasma (approximately 3 l).

The terminal half-life is approximately 6 hours and the volume of distribution at steady state is about 8 litres. This indicates a low iron distribution in the body fluid. A competitive exchange of iron to transferrin is observed due to the lower stability of iron (III)-hydroxide sucrose complex in comparison to transferrin. This results in an iron transport of approximately 31 mg iron over 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 about 75 % of the sucrose is excreted and the plasma levels of iron are reduced to the pre-dose iron levels.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injection

Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

EQUIFER must not be mixed with any other medicines except those mentioned in section 6.6.

6.3 Shelf life

3 years.

Shelf-life after opening and dilution:

From a microbiological point of view, EQUIFER should be used immediately after opening.

EQUIFER diluted with 0,9 % sodium chloride solution must be used within 12 hours.

6.4 Special precautions for storage

Store in a cool dark place at or below 25 °C.

Store in the carton until removed for use.

Do not freeze.

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

6.5 Nature and contents of container

5 ml clear glass ampoules in packs of 5 ampoules.

6.6 Special precautions for disposal and other handling

Ampoules should be visually inspected for damage before use and only those with sediment free solution may be used.

EQUIFER must not be mixed with other medicines for simultaneous administration. A 0,9 % sodium chloride solution is the only recommended diluent for an infusion.

Residual contents must be discarded, once the ampoule has been opened.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Equity Pharmaceuticals (Pty) Ltd

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Route 21 Corporate Park
Nellmapius Drive, Irene
Pretoria

8 REGISTRATION NUMBERS

45/8.3/0335

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05 December 2013

10 DATE OF REVISION OF THE TEXT

01 October 2021