1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINAL PRODUCT

FERINJECT®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One milliliter of solution contains 50 mg of iron as ferric carboxymaltose.

Each 10 ml vial contains 500 mg of iron as ferric carboxymaltose.

Excipient with known effect

One milliliter of solution contains up to 0,24 mmol (5,5 mg) sodium.

For the full list of excipients, see **Section 6.1**.

3. PHARMACEUTICAL FORM

Solution for injection/infusion. A dark brown, non-transparent, aqueous solution for injection/infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ferinject® is indicated for treatment of iron deficiency in adults when oral iron preparations are ineffective or cannot be used. The diagnosis must be based on laboratory tests.

4.2 Posology and method of administration

Safety of repeated dose during pregnancy has not been established.

Posology

Calculation of the cumulative dose

The adequate cumulative dose of **Ferinject®** must be calculated for each patient individually and must not be exceeded. For overweight patients, a normal body weight/blood volume relation should be assumed when determining the iron requirement. The dose of **Ferinject®** is expressed in mg of elemental iron.

The cumulative dose required for haemoglobin restoration and repletion of iron stores is calculated by the following Ganzoni formula:

Cumulative iron deficit [mg] =

body weight [kg] x (target Hb - actual Hb) [g/dl]** x 2,4*** + iron storage depot [mg]*****

* *Target Hb for body weight below 35 kg = 13 g/dl respectively 8,1 mmol/l.*

Target Hb for body weight 35 kg and above = 15 g/dl respectively 9,3 mmol/l.

** *To convert Hb [mM] to Hb [g/dl]: multiply Hb [mM] by the factor 1,61145.*

*** *Factor 2,4 = 0,0034 x 0,07 x 10000,*

0,0034: iron content of haemoglobin ≙ 0,34 %;

0,07: blood volume ≙ 7 % of body weight;

10000: conversion factor 1 g/dl =10000 mg/l.

**** *Depot iron for body weight below 35 kg = 15 mg/kg body weight.*

Depot iron for body weight 35 kg and above = 500 mg.

For patients ≤ 66 kg: the calculated cumulative dose is to be rounded down to the nearest 100 mg.

For patients > 66 kg: the calculated cumulative dose is to be rounded up to the nearest 100 mg.

Patients may continue to require therapy with **Ferinject®** at the lowest dose necessary to maintain target levels of haemoglobin, and other laboratory values of iron storage parameters within acceptable limits.

Maximum tolerated single dose

The adequate cumulative dose of **Ferinject®** must be calculated for each patient individually and must not be exceeded.

Since **Ferinject®** is an alkaline solution, it must never be given via a subcutaneous or intramuscular route. Paravenous leakage at the administration site must be avoided as leakage may cause pain, inflammation, tissue necrosis, sterile abscess or brown discolouration of the skin

Intravenous bolus injection:

Ferinject® may be administered by intravenous injection up to a maximum single dose of 4 ml (200 mg of iron) per day but not more than three times a week.

Test dose:

Before therapeutic dose is given to a new patient, a test dose of 10 ml to 15 ml (20 mg to 30 mg) of diluted Ferinject® should be given intravenously. If no adverse reaction occurs within 15 minutes, the remaining portion of the initial dose may be given (see Dilution plan of Ferinject®)

Intravenous drip infusion:

Ferinject® may be administered by intravenous infusion up to a maximum single dose of 20 ml of **Ferinject®** (1000 mg of iron) but not exceeding 0,3 ml of **Ferinject®** (15 mg of iron) per kg body weight or the calculated cumulative dose. Do not administer 20 ml (1000 mg of iron) as an infusion more than once a week.

The use of **Ferinject®** has not been studied in children, and is therefore not recommended in children under 18 years.

Method of administration

Ferinject® must be administered only by the intravenous route as a drip infusion. In a drip infusion, **Ferinject®** must be diluted only in sterile 0,9 % sodium chloride solution as follows:

Dilution plan of Ferinject® for intravenous drip infusion			
Ferinject®	Iron	Maximum amount of sterile 0,9 % sodium chloride solution	Minimum administration time
2 to < 4 ml	100 to < 200 mg	50 ml	-
4 to < 10 ml	200 to < 500 mg	100 ml	6 minutes
10 to 20 ml	500 to 1000 mg	250 ml	15 minutes

Note: For stability reasons, dilutions to concentrations less than 2 mg iron/ml are not permissible.

Ferinject® can only be administered as a bolus injection during a haemodialysis session. In this method, direct injection into the venous limb of the dialyzer should be used.

Ferinject® must not to be administered by the intramuscular route.

Incompatibilities

Ferinject® must not be mixed with other medicinal products. The compatibility with containers other than polyethylene and glass is not known. **Ferinject®** must only be mixed with sterile

0,9 % sodium chloride solution. No other intravenous dilution solutions and therapeutic agents should be used, as there is the potential for precipitation and/or interaction (See **INTERACTIONS**).

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

Each vial of **Ferinject®** is intended for single use only. Any unused product or waste material should be discarded.

Shelf-life after first opening of the container:
From a microbiological point of view, preparations for parenteral administration should be used immediately.

Shelf-life after dilution with sterile 0,9 % sodium chloride solution:
From a microbiological point of view, preparations for parenteral administration should be used immediately after dilution with sterile 0,9 % sodium chloride solution.

4.3 Contraindications

The use of **Ferinject®** is contraindicated in cases of:

- known hypersensitivity to ferric carboxymaltose or to any of the excipients
- anaemia not attributed to iron deficiency, e.g. other microcytic anaemia
- evidence of iron overload or disturbances in utilisation of iron
- pregnancy in the first trimester

4.4 Special warnings and precautions for use

Special warnings

Parenterally administered iron preparations can cause hypersensitivity reactions including anaphylactoid reactions, which may be potentially fatal (see section pre-clinical safety data). Therefore, facilities for cardio-pulmonary resuscitation must be available.

Parenteral administration of iron must be avoided in patients with hepatic dysfunction, particularly patients with Porphyria Cutanea Tarda where iron overload is a precipitating factor. Careful monitoring of iron status is recommended to avoid iron overload. It is known that the application of Ferinject® may cause transient increases in liver enzymes. In case clinically significant changes in liver enzymes occur, the therapy with Ferinject® should be discontinued, and reinstitution of therapy can be considered once liver enzymes have returned to baseline levels.

Parenteral iron must be used with caution in cases of acute or chronic infection, asthma, eczema or atopic allergies. It is recommended that the administration of **Ferinject®** is stopped in patients with ongoing bacteraemia.

The use of **Ferinject®** has not been studied in children under 18 years of age.

Precautions

Caution should be exercised to avoid paravenous leakage when administering **Ferinject®**. Paravenous leakage of **Ferinject®** at the injection site may lead to brown discolouration and irritation of the skin. In case of paravenous leakage, the administration of **Ferinject®** must be stopped immediately.

One millilitre of undiluted **Ferinject®** contains up to 0,24 mmol (5,5 mg) of sodium. This has to be taken into account in patients on a sodium-controlled diet.

Hypophosphataemic osteomalacia

Symptomatic hypophosphataemia leading to osteomalacia and fractures requiring clinical intervention including surgery has been reported in the post marketing setting. Patients should be asked 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 for hypophosphataemia. In case of persisting hypophosphataemia, treatment with **Ferinject®** should be re-evaluated.

4.5 Interaction with other medicinal products and other forms of interaction

The absorption of oral iron is reduced when administered concomitantly.

Ferinject® must not be mixed with other medicinal products. The compatibility with containers other than polyethylene and glass is not known. **Ferinject®** must only be mixed with sterile 0,9 % sodium chloride solution. No other intravenous dilution solutions and therapeutic agents should be used, as there is the potential for precipitation and/or interaction **(see Section 4.2**).

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established. **Ferinject®** should not be used in the first trimester of pregnancy.

Animal data suggest that iron released from **Ferinject®** can cross the placental barrier and that its use during pregnancy may influence skeletal development in the foetus.

Breast-feeding

Safety in lactation has not been established. Clinical studies showed that transfer of iron from **Ferinject®** to human milk was negligible (≤ 1 %). Based on data from 200 breastfed infants whose mothers received **Ferinject®**, it is unlikely to represent a risk to the nursing child.

4.7 ***Effects on ability to drive and use machines:***

After the patient received **Ferinject®,** he/she may feel dizzy, confused or lightheaded. **Ferinject®** may impair the ability to drive or operate machines.

Sodium content in excipients

This medicine contains 5,5 mg sodium per one milliliter of solution, which is less than the maximum daily intake of 2 g sodium for an adult which WHO recommends.

4.8 Undesirable effects

The most commonly reported side-effect is headache, occurring in 3,3 % of the patients.

Within the following table, side-effects are ranked under the following frequency classification:

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), including isolated reports.

System Organ Class	Frequency		
	Common	**Uncommon**	**Rare**
Immune system disorders		Hypersensitivity including anaphylactoid reactions	

Nervous system disorders	Headache, dizziness	Paraesthesia	
Vascular disorders		Hypotension, flushing	
Respiratory, thoracic and mediastinal disorders			Dyspnoea
Gastrointestinal disorders	Nausea, abdominal pain, constipation, diarrhoea	Dysgeusia, vomiting, dyspepsia, flatulence	
Skin and subcutaneous tissue disorders	Rash	Pruritus, urticaria	
Musculoskeletal and connective tissue disorders		Myalgia, back pain, arthralgia	Hypophosphataemic osteomalacia
General disorders and administration site conditions	Injection Site Reactions	Pyrexia, fatigue, chest pain, rigors, malaise, peripheral oedema	
Investigations	Decrease of blood phosphorus, increased alanine aminotransferase	Increased Aspartate aminostransferase, increased gamma-glutamyltransferase, increased blood lactate dehydrogenase	

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via "**6.04 Adverse Drug Reactions Reporting Form**" found online under SAHPRA's publications:

http://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Administration of **Ferinject®** in quantities exceeding the amount needed to correct iron deficit at the time of administration may lead to accumulation of iron in storage sites eventually leading to haemosiderosis. Monitoring of iron parameters such as serum ferritin and transferrin saturation may assist in recognising iron accumulation.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

A 8.3 Erythropoietics (haematinics)

Mechanism of Action

Pharmacodynamic effects

Ferinject® solution for injection/infusion contains iron in a stable ferric state as a complex with a carbohydrate polymer designed to release utilisable iron to the iron transport and storage proteins in the body (ferritin and transferrin).

Using positron emission tomography (PET) it was demonstrated that red cell utilisation of ^{59}Fe and ^{52}Fe from **Ferinject®** ranged from 61 % to 99 %. Patients with iron deficiency showed utilisation of radio-labelled iron of 91 % to 99 % after 24 days, and patients with renal anaemia showed utilisation of radiolabelled iron of 61 % to 84 % after 24 days.

Clinical efficacy and safety

Hypophosphataemia

Parenterally administered iron preparations can cause hypophosphataemia which in most cases is transient and without clinical symptoms. Incidental cases of hypophosphataemia requiring medical attention were reported, mainly in patients with existing risk factors and after prolonged exposure to high-dose IV iron.

Pharmacokinetic properties

Using positron emission tomography (PET) it was demonstrated that ^{59}Fe and ^{52}Fe from **Ferinject®** was rapidly eliminated from the blood, transferred to the bone marrow, and deposited in the liver and spleen.

After administration of a single dose of **Ferinject®** of 100 to 1000 mg of iron in iron deficient patients, maximum iron levels of 37 µg/ml up to 333 µg/ml after 15 minutes to 1,21 hours respectively are obtained. The volume of the central compartment corresponds well to the volume of the plasma (approximately 3 litres).

The iron injected or infused was rapidly cleared from the plasma, the terminal half-life ranged from 7 to 12 hours, the mean residence time (MRT) from 11 to 18 hours. Renal elimination of iron was negligible.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections

Ferinject® solution: pH = 5,0-7,0, Osmolarity = 480 mosm/l.

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines except those mentioned in **Section 6.6**. The compatibility with containers other than polyethylene and glass is not known.

6.3 Shelf life

3 years.

Shelf life after first opening of the container:

From a microbiological point of view, preparations for parenteral administration should be used immediately.

Shelf life after dilution with sterile 0,9 % m/V sodium chloride solution:

From a microbiological point of view, preparations for parenteral administration should be used immediately after dilution with sterile 0,9 % m/V sodium chloride solution.

6.4 Special precautions for storage

Store in the original package.

Store at or below 30 °C.

Do not freeze.

For storage conditions after reconstitution and dilution of the medicine, see **section 6.3.**

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

10 ml of solution is packed in a vial (type I glass) with a red bromobutyl rubber stopper and aluminium grey cap and plastic disk in a pack size of 1 vial.

6.6 Special precautions for disposal and other handling

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

Each vial of **Ferinject®** is intended for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

Ferinject® must only be mixed with sterile 0,9 % m/V sodium chloride solution. No other intravenous dilution solutions and therapeutic agents should be used, as there is the potential for precipitation and/or interaction. For dilution instructions, see section 4.2.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Holder of Certificate of Registration

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

Hotline: 0800 118 088

8. REGISTRATION NUMBER(S)

45/8.3/0948

9. DATE OF PACKAGE INSERT FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06 March 2014

10. DATE OF REVISION OF THE TEXT

05 July 2021

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