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 (see section 5.1):

- Oral iron preparations are ineffective or cannot be used.
- There is a clinical need to deliver iron rapidly.

The diagnosis of iron deficiency must be based on laboratory tests.

4.2 Posology and method of administration

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

FERINJECT® 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. The patient should be observed for adverse effects for at least 30 minutes following each FERINJECT® administration (see section 4.4).

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.

Posology

The posology of FERINJECT® follows a stepwise approach:

[1] Determination of the individual iron need.

[2] Calculation and administration of the iron dose(s).

[3] Post-iron repletion assessments.

These steps are outlined below:

Step 1: Determination of the iron need

The individual iron need for repletion using FERINJECT® is determined based on the patient's body weight and haemoglobin (Hb) level. Refer to Table 1 for determination of the iron need:

Table 1: Determination of the iron need

Hb		**Patient body weight**		
g/dL	**mmol/L**	**below 35 kg**	**35 kg to < 70 kg**	**70 kg and above**
< 10	< 6,2	500 mg	1 500 mg	2 000 mg
10 to < 14	6,2 to < 8,7	500 mg	1 000 mg	1 500 mg
≥ 14	≥ 8,7	500 mg	500 mg	500 mg

Iron deficiency must be confirmed by laboratory tests as stated in 4.1 (see section 4.1).

Step 2: Calculation and administration of the maximum individual iron dose(s)

Based on the iron need determined above the appropriate dose(s) of FERINJECT® should be administered taking into consideration the following:

A single FERINJECT® administration should not exceed:

(a) 15 mg/kg body weight (for administration by intravenous injection) or 20 mg iron/kg body weight (for administration by intravenous infusion).

(b) 1 000 mg of iron (20 mL FERINJECT®)

The maximum recommended cumulative dose of FERINJECT® is 1000 mg of iron (20 mL FERINJECT®) per week.

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 FERINJECT® administration to allow adequate time for erythropoiesis and iron utilization. In the event the patient requires further iron repletion, the iron need should be recalculated using Table 1 above (see section 5.1).

Special Populations

Patients with haemodialysis-dependent chronic kidney disease

A single maximum daily dose of 200 mg iron should not be exceeded in haemodialysis-dependent chronic kidney disease patients (see also section 4.4).

Elderly population

Ferric carboxymaltose has been administered to over 2,000 elderly patients (≥ 65 years of age) according to the approved dosing regimen: injections/infusions of ≤ 1,000 mg iron, not more than once per week (non-dialysis-dependent chronic kidney disease, inflammatory bowel disease and chronic heart failure studies), or as bolus injections of ≤ 200 mg iron, not more than 3 times per week (haemodialysis-dependent chronic kidney disease and chronic heart failure studies). No special dosage or administration guidelines were applied to elderly patients in these studies, and the dosing schedules were not associated with any significant safety concerns.

Paediatric population

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

Method of administration

FERINJECT® must only be administered by the intravenous route:

- by injection, or
- by infusion (diluted only in sterile 0,9 % sodium chloride solution), or
- as a bolus injection, undiluted during a haemodialysis session , by direct injection into the venous limb of the dialyzer.

Since FERINJECT® is an alkaline solution, it must not be administered by the 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 (see section 4.8)

Intravenous injection

FERINJECT® may be administered by intravenous injection using undiluted solution. The maximum single dose is 15 mg iron/kg body weight but should not exceed 1 000 mg iron. The administration rates are as shown in Table 2:

Table 2: Administration rates for intravenous injection of FERINJECT®

Volume of FERINJECT® required	Equivalent iron dose	Administration rate / Minimum administration time
2 to 4 mL	100 to 200 mg	No minimal prescribed time
>4 to 10 mL	>200 to 500 mg	100 mg iron/min
>10 to 20 mL	>500 to 1000 mg	15 minutes

Intravenous infusion

FERINJECT® may be administered by intravenous infusion, in which case it must be diluted. The maximum single dose is 20 mg iron/kg body weight, but should not exceed 1,000 mg iron.

For infusion, FERINJECT® must only be diluted in sterile 0, 9 % *m/v* sodium chloride solution as shown in Table 3. Note: for stability reasons, FERINJECT® should not be diluted to concentrations less than 2 mg iron/mL (not including the volume of the ferric carboxymaltose solution). For further instructions on dilution of the medicinal product before administration, see section 6.6.

Table 3: Dilution plan of FERINJECT® for intravenous infusion

Volume of FERINJECT® required	Equivalent iron dose	Maximum amount of sterile 0,9 % m/V sodium chloride solution	Minimum administration time
2 to 4 mL	100 to 200 mg	50 mL	No minimal prescribed time
>4 to 10 mL	>200 to 500 mg	100 mL	6 minutes
>10 to 20 mL	>500 to 1000 mg	250 mL	15 minutes

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.

4.3 Contraindications

The use of FERINJECT® is contraindicated in cases of:

- Known hypersensitivity to ferric carboxymaltose, other parenteral iron products or to any of the excipients (see section 6.1).
- Anaemia not attributed to iron deficiency, e.g. other microcytic anaemia.
- Evidence of iron overload or disturbances in utilisation of iron.

4.4 Special warnings and precautions for use

Hypersensitivity reactions

Parenterally administered iron preparations can cause hypersensitivity reactions including serious and potentially fatal anaphylactic/anaphylactoid reactions, (see section pre-clinical safety data). Hypersensitivity reactions have also been reported after previously uneventful doses of parenteral iron complexes (see section 4.8). 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). The risk 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). Therefore, facilities for cardio-pulmonary resuscitation must be available. FERINJECT® should only be administered when staff trained to evaluate and manage anaphylactic reactions are 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 FERINJECT® administration. 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.

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.

Hepatic and renal impairment

In patients with liver dysfunction, parenteral iron should only be administered after careful benefit/risk assessment. Parenteral administration of iron must be avoided in patients with hepatic dysfunction, particularly patients with Porphyria Cutanea Tarda (PCT) 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.

No safety data on haemodialysis-dependent chronic kidney disease patients receiving single doses of more than 200 mg iron are available.

Infection

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. Therefore, in patients with chronic infection a benefit/risk evaluation has to be performed, taking into account the suppression of erythropoiesis.

Paediatric population

The use of FERINJECT® has not been studied and should not be used in children under 18 years of age (see section 4.2).

Extravasation

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

Excipients:

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

4.5 Interaction with other medicinal products and other forms of interaction

The absorption of oral iron is reduced when administered concomitantly with parenteral iron preparations. Therefore, if required, oral iron therapy should not be started for at least 5 days after the last administration of FERINJECT®.

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 sections 4.2, 6.2 and 6.6).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of FERINJECT® in pregnant women (see section 5.1). A careful benefit/risk evaluation is required before use during pregnancy and FERINJECT® should not be used during pregnancy unless clearly necessary.

Iron deficiency occurring in the first trimester of pregnancy can in many cases be treated with oral iron. Treatment with FERINJECT® 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 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 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 (see section 5.3).

Breastfeeding

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.

Fertility

There are no data on the effect of FERINJECT® on human fertility. Fertility was unaffected

following FERINJECT® treatment in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

FERINJECT® may have a moderate influence on the patient.

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

4.8 Undesirable effects

a) Summary of the safety profile

Table 4 presents the adverse drug reactions (ADRs) reported during clinical studies in which > 8 000 patients received FERINJECT®, as well as those reported from the post-marketing experience (see table footnotes for details).

The most commonly reported ADR is nausea (occurring in 2,9 % of the patients), followed by injection/infusion site reactions, hypophosphataemia, headache, flushing, dizziness and hypertension. Injection/infusion site reactions comprise several ADRs which individually are either uncommon or rare.

The most serious ADR is anaphylactoid/anaphylactic reactions (rare); fatalities have been reported. See section 4.4 for further details.

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	Common	Uncommon	Rare	Frequency unknown
Immune system disorders		Hypersensitivity including anaphylactoid reactions		
Metabolism	Hypophosphataemia			

and nutrition disorders				
Psychiatric disorders			Anxiety[2]	
Nervous system disorders	Headache, dizziness	Paraesthesia, dysgeusia		Loss of consciousness [1]
Cardiac disorders		Tachycardia		Kounis syndrome[1]
Vascular disorders	Flushing, hypertension	Hypotension	Phlebitis, syncope[2], presyncope[2]	
Respiratory, thoracic and mediastinal disorders		Dyspnoea	Bronchospasm	
Gastrointestinal disorders	Nausea	Dysgeusia, vomiting, dyspepsia, abdominal pain, constipation, diarrhoea	Flatulence	
Skin and subcutaneous tissue disorders		Pruritus, urticaria, erythema, rash	Angioedema[2], pallor[2] distant skin discolouration[2]	Face oedema[1]
Musculoskeletal and connective tissue disorders		Myalgia, back pain, arthralgia, pain in extremity, muscle spasms		Hypophosphataemic osteomalacia[1]
General disorders and administration site conditions	Injection/infusion site reactions	Pyrexia, fatigue, chest pain, rigors, peripheral oedema	Malaise, influenza like illness (whose onset may vary from a few hours to several days) [2]	
Investigations	Decrease of blood phosphorus,	Increased aspartate aminostransferase, increased gamma-glutamyltransferase, increased blood lactate dehydrogenase, increased alanine aminotransferase, increased blood alkaline phosphatase		

[1] ADRs exclusively reported in the post-marketing setting; estimated as rare.
[2] ADRs reported in the post-marketing setting which are also observed in the clinical setting.
[3] Includes the following preferred terms: rash (individual ADR determined to be uncommon) and rash erythematous, -generalised, -macular, -maculo-papular, -pruritic (all individual ADRs determined to be rare).
[4] Includes, but is not limited to, the following preferred terms: injection/infusion site -pain, -haematoma, -discolouration, -extravasation, -irritation, -reaction, (all individual ADRs determined to be uncommon) and -paraesthesia (individual ADR determined to be rare).

Note: ADR = Adverse drug reaction.

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 Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

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. If iron accumulation has occurred, treat according to standard medical practice, e.g. consider the use of an iron chelator.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

A 8.3 Erythropoietics (haematinics)

Pharmacotherapeutic group: Irone trivalent, parenteral preparation, ATC code: B03AC

Mechanism of Action

FERINJECT® is a colloidal solution of the iron complex ferric carboxymaltose.

Pharmacodynamic effects

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

FERINJECT® treatment results in an increase in reticulocyte count, serum ferritin levels and TSAT levels to within normal ranges.

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 studies have shown that the haematological response and the repletion of the iron stores is faster after intravenous administration of ferric carboxymaltose than with orally administered comparators.

Clinical efficacy and safety

The efficacy and safety of FERINJECT® has been studied in different therapeutic areas necessitating intravenous iron to correct iron deficiency. The main studies are described in more detail below.

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.

Cardiology

Chronic heart failure

Study CONFIRM-HF was a double-blind, randomised, 2-arm study comparing FERINJECT® (n=150) vs. placebo (n=151) in patients with chronic heart failure and ID for a treatment period of 52 weeks. At Day 1 and Week 6 (correction phase), patients received either FERINJECT® according to a simplified dosing grid using baseline Hb and body weight at screening (see section 4.2), placebo or no dose. At Weeks 12, 24, and 36 (maintenance phase) patients received FERINJECT® (500 mg iron) or placebo if serum ferritin was <100 ng/mL or 100 to 300 ng/mL with TSAT < 20 %. The treatment benefit of FERINJECT® vs. placebo was demonstrated with the primary efficacy endpoint, the change in the 6-minute walk test (6MWT) from baseline to Week 24 (33 ±11 meters, p=0,002). This effect was sustained throughout the study to Week 52 (36 ±11 meters, p<0,001).

Study EFFECT-HF was an open-label (with blinded endpoint evaluation), randomised, 2-arm study comparing FERINJECT® (n=86) vs. standard of care (n=86) in patients with chronic heart failure and ID for a treatment period of 24 weeks. At Day 1 and Week 6 (correction phase), patients received either FERINJECT® according to a simplified dosing grid using baseline Hb and body weight at screening (see section 4.2) or standard of care. At Week 12, (maintenance phase) patients received FERINJECT® (500 mg iron) or standard of care if serum ferritin <100 ng/ml or 100 to 300 ng/ml and TSAT < 20 %. The treatment benefit of FERINJECT® vs. standard of care was demonstrated with the primary efficacy endpoint, the change in weight-adjusted peak VO_2 from baseline to Week 24 (LS Mean 1,04 ±0,44, p=0,02).

Nephrology

Haemodialysis-dependent chronic kidney disease

Study VIT-IV-CL-015 was an open-label, randomised parallel group study comparing FERINJECT® (n=97) to iron sucrose (n=86) in patients with ID anaemia undergoing haemodialysis. Patients received FERINJECT® or iron sucrose 2 to 3 times per week in single doses of 200 mg iron directly into the dialyser until the individually calculated cumulative iron dose was reached (mean cumulative dose of iron as FERINJECT®: 1,700 mg). The primary efficacy endpoint was the percentage of patients reaching an increase in Hb of ≥1,0 g/dL at 4 weeks after baseline. At 4 weeks after baseline, 44,1 % responded to treatment with FERINJECT®(i.e. Hb increase of ≥1,0 g/dL) compared to 35,3 % for iron sucrose (p=0,2254).

Non-dialysis-dependent chronic kidney disease

Study 1VIT04004 was an open-label, randomised active-control study, evaluating the safety and efficacy of FERINJECT® (n=147) vs. oral iron (n=103). Patients in the FERINJECT® group received 1,000 mg of iron at baseline and 500 mg of iron at days 14 and 28, if TSAT was < 30 % and serum ferritin was <500 ng/mL at the respective visit. Patients in the oral iron arm received 65 mg iron TID as ferrous sulphate from baseline to day 56. Patients were followed-up until day 56. The primary efficacy endpoint was the percentage of patients achieving an increase in Hb of ≥1,0 g/dL anytime between baseline and end of study or time of intervention. This was achieved by 60,54 % of patients receiving FERINJECT® vs. 34,7 % of patients in the oral iron group (p<0,001). Mean haemoglobin change to day 56/end of

study was 1,0 g/dL in the FERINJECT® group and 0,7 g/dL in the oral iron group (p=0,034, 95 % CI: 0,0; 0,7).

Gastroenterology

Inflammatory bowel disease

Study VIT-IV-CL-008 was a randomised, open-label study which compared the efficacy of FERINJECT® vs. oral ferrous sulphate in reducing ID anaemia in patients with inflammatory bowel disease (IBD). Patients received either FERINJECT® (n=111) in single doses of up to 1 000 mg iron once per week until the individually calculated iron dose (per Ganzoni formula) was reached (mean cumulative iron dose: 1,490 mg), or 100 mg iron BID as ferrous sulphate (n=49) for 12 weeks. Patients receiving FERINJECT® showed a mean increase in Hb from baseline to Week 12 of 3,83 g/dL, which was non-inferior to 12 weeks of twice daily therapy with ferrous sulphate (3,75 g/dL, p=0,8016).

Study FER-IBD-07-COR was a randomised, open-label study comparing the efficacy of FERINJECT® vs. iron sucrose in patients with remitting or mild IBD. Patients receiving FERINJECT® were dosed according to a simplified dosing grid using baseline Hb and body weight (see section 4.2) in single doses up to 1 000 mg iron, whereas patients receiving iron sucrose were dosed according to individually calculated iron doses using the Ganzoni formula in doses of 200 mg iron until the cumulative iron dose was reached. Patients were followed-up for 12 weeks. 65,8 % of patients receiving FERINJECT® (n=240; mean cumulative iron dose: 1,414 mg) vs. 53,6 % receiving iron sucrose (n=235; mean cumulative dose 1,207 mg; p=0,004) had responded at Week 12 (defined as Hb increase ≥2 g/dL). 83,8 % of FERINJECT®-treated patients vs. 75,9 % of iron sucrose-treated patients achieved a Hb increase ≥2 g/dL or had Hb within normal limits at Week 12 (p=0,019).

Women's health

Post-partum

Study VIT-IV-CL-009 was a randomised open-label non-inferiority study comparing the efficacy of FERINJECT®(n=227) vs. ferrous sulphate (n=117) in women suffering from post-partum anaemia. Patients received either FERINJECT® in single doses of up to 1 000 mg iron until their individually calculated cumulative iron dose (per Ganzoni formula) was reached, or 100 mg of iron as oral ferrous sulphate BID for 12 weeks. Patients were followed-up for 12 weeks. The mean change in Hb from baseline to Week 12 was 3,37 g/dL in the FERINJECT® group (n=179; mean cumulative iron dose: 1,347 mg) vs. 3,29 g/dL in the ferrous sulphate group (n=89), showing non-inferiority between the treatments.

Pregnancy

Intravenous iron medicines should not be used during pregnancy unless clearly necessary. Treatment with FERINJECT® 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 (see section 4.6).

Limited safety data in pregnant women are available from study FER-ASAP-2009-01, a randomised, open-label, study comparing FERINJECT® (n=121) vs. oral ferrous sulphate (n=115) in pregnant women in the second and third trimester with ID anaemia for a treatment period of 12 weeks. Patients received FERINJECT® in cumulative doses of 1 000 mg or 1 500 mg of iron (mean cumulative dose: 1 029 mg iron) based on Hb and body weight at screening, or 100 mg of oral iron BID for 12 weeks. The incidence of treatment related adverse events was similar between FERINJECT® treated women and those treated with oral iron (11,4 % FERINJECT® group; 15,3 % oral iron group). The most commonly reported treatment-related adverse events were nausea, upper abdominal pain and

headache. Newborn Apgar scores as well as newborn iron parameters were similar between treatment groups.

Ferritin monitoring after replacement therapy

There is limited data from study VIT-IV-CL-008 which demonstrates that ferritin levels decrease rapidly 2 to 4 weeks following replacement and more slowly thereafter. The mean ferritin levels did not drop to levels where retreatment might be considered during the 12 weeks of study follow up. Thus, the available data does not clearly indicate an optimal time for ferritin retesting although assessing ferritin levels earlier than 4 weeks after replacement therapy appears premature. Thus, it is recommended that further re-assessment of ferritin should be made by the clinician based on the individual patient's condition.

5.2 Pharmacokinetic properties

Distribution

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).

Elimination

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.

5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeat dose toxicity and genotoxicity. Preclinical studies indicate that iron released from FERINJECT® does cross the placental barrier and is excreted in milk in limited, controlled amounts. In reproductive toxicology studies using iron replete rabbits FERINJECT® was associated with minor skeletal abnormalities in the foetus. In a fertility study in rats, there were no effects on fertility for either male or female animals. No long-term studies in animals have been performed to evaluate the carcinogenic potential of FERINJECT®. No evidence of allergic or immunotoxic potential has been observed. A controlled in-vivo test demonstrated no cross-reactivity of FERINJECT® with anti-dextran antibodies. No local irritation or intolerance was observed after intravenous administration (see section 4.6)

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 to 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.

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

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

28 March 2025

Die Afrikaanse Professionele Inligting is op versoek beskikbaar. Mediese Blitslyn: 0800 118 088.

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