SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Fercarbos 50 mg iron/ml dispersion for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL of dispersion contains ferric carboxymaltose corresponding to 50 mg iron.

Each 2 mL vial contains ferric carboxymaltose corresponding to 100 mg iron.
Each 10 mL vial contains ferric carboxymaltose corresponding to 500 mg iron.
Each 20 mL vial contains ferric carboxymaltose corresponding to 1 000 mg iron.

Excipient with known effect
One mL of dispersion contains up to 5.5 mg (0.24 mmol) sodium, see section 4.4.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for injection/infusion.

Dark brown opaque aqueous dispersion.
pH between 5 to 7
Osmolality between 280 mOsmol/Kg and 385 mOsmol/Kg

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fercarbos is indicated for the treatment of iron deficiency when (see section 5.1):

- oral iron preparations are ineffective.
- oral iron preparations 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

Carefully monitor patients for signs and symptoms of hypersensitivity reactions during and following each administration of Fercarbos.

Fercarbos 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 treatment administration (see section 4.4).

Posology

The posology of Fercarbos follows a stepwise approach: [1] determination of the individual iron need, [2] calculation and administration of the iron dose(s), and [3] post-iron repletion assessments. These steps are outlined below:

Step 1: Determination of the iron need
The individual iron need for repletion using Fercarbos is determined based on the patient's body weight and haemoglobin (Hb) level. Refer to Table 1 for determination of the total iron need. 2 doses may be required to replenish the total iron need, see Step 2 for the maximum individual iron doses. Iron deficiency must be confirmed by laboratory tests as stated in 4.1.

Table 1: Determination of the total 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	30 mg/kg body weight	1 500 mg	2 000 mg
10 to <14	6.2 to <8.7	15 mg/kg body weight	1 000 mg	1 500 mg
≥14	≥8.7	15 mg/kg body weight	500 mg	500 mg

Step 2: Calculation and administration of the maximum individual iron dose(s)
Based on the total iron need determined, the appropriate dose(s) of Fercarbos should be administered taking into consideration the following:

Adults and adolescents aged 14 years and older

A single Fercarbos administration should not exceed:
- 15 mg iron/kg body weight (for administration by intravenous injection) or 20 mg iron/kg body weight (for administration by intravenous infusion)
- 1 000 mg of iron (20 mL Fercarbos)

The maximum recommended cumulative dose of Fercarbos is 1 000 mg of iron (20 mL Fercarbos) per week. If the total iron need is higher, then the administration of an additional dose should be a minimum of 7 days apart from the first dose.

Children and adolescents aged 1 to 13 years

A single Fercarbos administration should not exceed:
- 15 mg iron/kg body weight
- 750 mg of iron (15 mL Fercarbos)

The maximum recommended cumulative dose of Fercarbos is 750 mg of iron (15 mL Fercarbos) per week. If the total iron need is higher, then the administration of an additional dose should be a minimum of 7 days apart from the first dose.

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 treatment administration to allow adequate time for erythropoiesis and iron utilisation. In the event the patient requires further iron repletion, the iron need should be recalculated (see Step 1).

Children below 1 year of age
The efficacy and safety of Fercarbos has not been investigated in children below 1 year of age. This medicinal product is therefore not recommended for use in children in this age group.

Patients with haemodialysis-dependent chronic kidney disease
In adults and adolescents aged 14 years and older, 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).

In children aged 1 to 13 years with chronic kidney disease requiring haemodialysis, the efficacy and safety of Fercarbos has not been investigated. This medicinal product is therefore not recommended for use in children aged 1 to 13 years with chronic kidney disease requiring haemodialysis.

Method of administration

Fercarbos must only be administered by the intravenous route:

- by injection, or
- by infusion, or
- during a haemodialysis session undiluted directly into the venous limb of the dialyser.

Fercarbos must not be administered by the subcutaneous or intramuscular route.

Intravenous injection

Fercarbos may be administered by intravenous injection using undiluted dispersion. In adults and adolescents aged 14 years and older, the maximum single dose is 15 mg iron/kg body weight but should not exceed 1 000 mg of iron. In children aged 1 to 13 years, the maximum single dose is 15 mg iron/kg body weight, but should not exceed 750 mg of iron. The administration rates are as shown in Table 2:

Table 2: Administration rates for intravenous injection of Fercarbos

Volume of Fercarbos 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 1 000 mg	15 minutes

Intravenous infusion

Fercarbos may be administered by intravenous infusion, in which case it must be diluted. In adults and adolescents aged 14 years and older, the maximum single dose is 20 mg iron/kg body weight but should not exceed 1 000 mg of iron. In children aged 1 to 13 years, the maximum single dose is 15 mg iron/kg body weight, but should not exceed 750 mg of iron.

For infusion, Fercarbos must only be diluted in sterile sodium chloride 9 mg/mL (0.9%) solution as shown in Table 3. Note: for stability reasons, Fercarbos should not be diluted to concentrations less than 2 mg iron/mL (not including the volume of the ferric carboxymaltose dispersion). For further instructions on dilution of the medicinal product before administration, see section 6.6.

Table 3: Dilution plan of Fercarbos for intravenous infusion

Volume of Fercarbos required	Equivalent iron dose	Maximum amount of sterile sodium chloride 9 mg/mL (0.9%) 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 1 000 mg	250 mL	15 minutes

4.3 Contraindications

The use of Fercarbos is contraindicated in cases of:

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- known serious hypersensitivity to other parenteral iron products.
- anaemia not attributed to iron deficiency, e.g. other microcytic anaemia.
- evidence of iron overload or disturbances in the 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 reactions. Hypersensitivity reactions have also been reported after previously uneventful doses of parenteral iron complexes. 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 drug 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).

Fercarbos 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 treatment 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 reactions should be available, including an injectable 1:1 000 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 ferric carboxymaltose should be re-evaluated.

Hepatic or renal impairment
In patients with liver dysfunction, parenteral iron should only be administered after careful benefit/risk assessment. Parenteral iron administration should be avoided in patients with hepatic dysfunction where iron overload is a precipitating factor, in particular Porphyria Cutanea Tarda (PCT). Careful monitoring of iron status is recommended to avoid iron overload.

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 case of acute or chronic infection, asthma, eczema or atopic allergies. It is recommended that the treatment with ferric carboxymaltose 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.

Extravasation
Caution should be exercised to avoid paravenous leakage when administering ferric carboxymaltose . Paravenous leakage of this medicinal product at the administration site may lead to irritation of the skin and potentially long lasting brown discolouration at the site of administration. In case of paravenous leakage, the administration of Fercarbos must be stopped immediately.

Excipients
This medicinal product contains 5.5 mg (0.24 mmol) sodium per mL of undiluted dispersion, equivalent to 0.3% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

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 Fercarbos.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are limited data from the use of ferric carboxymaltose in pregnant women (see section 5.1). Animal data suggest that iron released from ferric carboxymaltose can cross the placental barrier and that its use during pregnancy may influence skeletal development in the foetus (see section 5.3).

Fercabos should not be used during the first trimester of pregnancy. Iron deficiency occurring in the first trimester of pregnancy can in many cases be treated with oral iron. Treatment with Fercarbos should be confined to the second and third trimester and should only be used 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.

Breast-feeding
Clinical studies showed that transfer of iron from ferric carboxymaltose to human milk was negligible (≤1%). Based on limited data on breast-feeding women it is unlikely that ferric carboxymaltose represents a risk to the breast-fed child. Fercarbos can be used during breast-feeding.

Fertility
There are no data on the effect of ferric carboxymaltose on human fertility. Fertility was unaffected following ferric carboxymaltose treatment in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Fercarbos has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Table 4 presents the adverse drug reactions (ADRs) reported during clinical studies in which >9 000 subjects (including > 100 children and adolescents aged 1 to 17 years) received ferric carboxymaltose as well as those reported from the post-marketing experience (see table footnotes for details).

The most commonly reported ADR is nausea (occurring in 3.2% of the subjects), 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 anaphylactic reactions (rare); fatalities have been reported. See section 4.4 for further details.

Table 4: Adverse drug reactions observed during clinical trials and post-marketing experience

System Organ Class	Common (≥1/100 to <1/10)	Uncommon (≥1/1 000 to <1/100)	Rare (≥1/10 000 to <1/1 000)	Frequency not known[1]
Immune system disorders		Hypersensitivity	Anaphylactic reactions	
Metabolism and nutritional disorders	Hypophosphataemia			
Nervous system disorders	Headache, dizziness	Paraesthesia, dysgeusia		Loss of consciousness[1]
Psychiatric disorders			Anxiety[2]	
Cardiac disorders		Tachycardia		Kounis syndrome[1]
Vascular disorders	Flushing, hypertension	Hypotension	Phlebitis, syncope[2], presyncope[2]	
Respiratory, thoracic and mediastinal disorders		Dyspnoea	Bronchospasm[2]	
Gastrointestinal disorders	Nausea	Vomiting, dyspepsia, abdominal pain, constipation, diarrhoea	Flatulence	
Skin and subcutaneous tissue disorders		Pruritus, urticaria, erythema, rash[3]	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[4]	Pyrexia, fatigue, chest pain, oedema peripheral, chills, malaise	Influenza like illness (whose onset may vary from a few hours to several days) [2]	
Investigations		Alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, blood lactate dehydrogenase increased, blood		

		alkaline phosphatase increased		

(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.

Paediatric population
The safety profile for children and adolescents aged 1 to 17 years is comparable with that of adults. 110 paediatric patients received ferric carboxymaltose in 7 clinical studies. No serious ADRs were reported. The reported non-serious ADRs were hypophosphataemia (n = 5), urticaria (n = 5), injection/infusion site reactions (n = 4), abdominal pain (n = 2), flushing (n = 2), headache (n = 2), pyrexia (n = 2), liver enzymes increased (n = 2) and rash (n = 2). Constipation, gastritis, hypertension, pruritus and thirst were reported only once.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via [To be completed nationally].

4.9 Overdose

Administration of Fercarbos 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 (TSAT) 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: Iron trivalent, parenteral preparation, ATC code: B03AC

Fercarbos dispersion for injection/infusion is a colloidal solution of the iron complex ferric carboxymaltose.

The complex is designed to provide, in a controlled way, utilisable iron for the iron transport and storage proteins in the body (transferrin and ferritin, respectively).

Red cell utilisation of ^{59}Fe from radio- ferric carboxymaltose ranged from 91% to 99% in subjects with iron deficiency (ID) and 61% to 84% in subjects with renal anaemia at 24 days post-dose. Ferric carboxymaltose treatment results in an increase in reticulocyte count, serum ferritin levels and TSAT levels to within normal ranges.

Clinical efficacy and safety

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

Cardiology

Chronic heart failure
Study CONFIRM-HF was a double-blind, randomised, 2-arm study comparing ferric carboxymaltose (n=150) vs. placebo (n=151) in subjects with chronic heart failure and ID for a treatment period of 52 weeks. At Day 1 and Week 6 (correction phase), subjects received either ferric carboxymaltose 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) subjects received ferric carboxymaltose (500 mg iron) or placebo if serum ferritin was <100 ng/mL or 100 to300 ng/mL with TSAT <20%. The treatment benefit of ferric carboxymaltose 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 metres, p=0.002). This effect was sustained throughout the study to Week 52 (36 ±11 metres, p<0.001).

Study EFFECT-HF was an open-label (with blinded endpoint evaluation), randomised, 2-arm study comparing ferric carboxymaltose (n=86) vs. standard of care (n=86) in subjects with chronic heart failure and ID for a treatment period of 24 weeks. At Day 1 and Week 6 (correction phase), subjects received either ferric carboxymaltose 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) subjects received ferric carboxymaltose (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 ferric carboxymaltose 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 ferric carboxymaltose (n=97) to iron sucrose (n=86) in subjects with ID anaemia undergoing haemodialysis. Subjects received ferric carboxymaltose or iron sucrose 2-3 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 ferric carboxymaltose: 1 700 mg). The primary efficacy endpoint was the percentage of subjects 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 ferric carboxymaltose (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 ferric carboxymaltose (n=147) vs. oral iron (n=103). Subjects in the ferric carboxymaltose 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. Subjects in the oral iron arm received 65 mg iron TID as ferrous sulphate from baseline to day 56. Subjects were followed-up until day 56. The primary efficacy endpoint was the percentage of subjects 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 subjects receiving ferric carboxymaltose vs. 34.7% of subjects in the oral iron group (p<0.001). Mean haemoglobin change to day 56/end of study was 1.0 g/dL in the ferric carboxymaltose 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 ferric carboxymaltose vs. oral ferrous sulphate in reducing ID anaemia in subjects with inflammatory bowel disease (IBD). Subjects received either ferric carboxymaltose (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. Subjects receiving ferric carboxymaltose 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 ferric carboxymaltose vs. iron sucrose in subjects with remitting or mild IBD. Subjects receiving ferric carboxymaltose 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 subjects 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. Subjects were followed-up for 12 weeks. 65.8% of subjects receiving ferric carboxymaltose (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 ferric carboxymaltose-treated subjects vs. 75.9% of iron sucrose-treated subjects 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 ferric carboxymaltose (n=227) vs. ferrous sulphate (n=117) in women suffering from post-partum anaemia. Subjects received either ferric carboxymaltose 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. Subjects were followed-up for 12 weeks. The mean change in Hb from baseline to Week 12 was 3.37 g/dL in the ferric carboxymaltose 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 medicinal products should not be used during pregnancy unless clearly necessary. Treatment with ferric carboxymaltose 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 ferric carboxymaltose (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. Subjects received ferric carboxymaltose 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 ferric carboxymaltose treated women and those treated with oral iron (11.4% ferric carboxymaltose 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.

Paediatric population

Adolescents aged 14 years or older were included in 4 studies performed in adults. In addition, paediatric studies were performed in children and adolescents aged 1 to 17 years with iron deficiency

anaemia. The most common aetiologies for iron deficiency anaemia were gastrointestinal diseases (e.g. inflammatory bowel disease, Helicobacter pylori gastritis, coeliacic disease) and heavy uterine bleeding.

In a prospective pharmacokinetic/pharmacodynamic phase 2 study (1VIT13036), 35 children at a median age of 9.8 years (range: 1.5-17.5 years) were treated in 2 consecutive dose cohorts with single doses of ferric carboxymaltose 7.5 mg iron/kg body weight (n = 16) or ferric carboxymaltose 15 mg iron/kg body weight (n = 19), at a maximum dose of 750 mg iron. Hb, ferritin and TSAT increased dose-dependently. On day 35 after injection, the mean (SD) increase in Hb was 1.9 (1.38) g/dL with ferric carboxymaltose 7.5 mg iron/kg and 2.8 (1.15) g/dL with ferric carboxymaltose 15 mg iron/kg. See also section 4.8.

In a prospective, open-label, parallel-group phase 3 study (1VIT17044), efficacy and safety of ferric carboxymaltose were compared with oral iron therapy. 40 children at a median age of 14.5 years (range:1 to 17 years) were treated with 2 doses of ferric carboxymaltose 15 mg iron/kg body weight at a 7-day interval (maximum single dose 750 mg) and 39 children at a median age of 14.0 years (range: 1 to 17 years) with oral ferrous sulphate for 28 days. A similar increase in Hb was observed after both treatment with ferric carboxymaltose and treatment with oral iron sulphate. The increase in Hb from baseline to day 35 (LS Mean [95%CI]) was 2.22 [1.69, 2.75] g/dL after ferric carboxymaltose and 1.92 [1.43, 2.41] g/dL after oral iron sulphate. In total, 87.5% of patients in the intravenous iron group achieved a Hb increase >1 g/dL at EOS. The increase in ferritin and TSAT, used as a measure for the replenishment of iron stores, was higher after intravenous iron therapy compared to oral iron sulphate therapy, with an increase in ferritin from baseline to day 35 (LS Mean [95%CI]) of 132.1 [105.44, 158.76] ng/mL after ferric carboxymaltose and 11.0 [-15.62, 37.65] ng/mL after oral iron sulphate. The corresponding increase in TSAT was 24.3 [19.19, 29.41] % and 8.7 [3.70, 13.63] %, respectively. See also section 4.8.

Ferritin monitoring after replacement therapy
There is limited data from study VIT-IV-CL-008 which demonstrates that ferritin levels decrease rapidly 2-4 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
Positron emission tomography demonstrated that ^{59}Fe and ^{52}Fe from ferric carboxymaltose 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 ferric carboxymaltose of 100 to 1 000 mg of iron in ID subjects, maximum total serum iron levels of 37 µg/mL up to 333 µg/mL are obtained after 15 minutes to 1.21 hours respectively. 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.

Paediatric population
The pharmacokinetic properties of ferric carboxymaltose at a dose of 15 mg iron/kg were similar to those for adult patients with iron deficiency. Serum iron increased proportionally to the dose after a single dose of 7.5 mg iron/kg or 15 mg iron/kg. After a single dose of ferric carboxymaltose of 15 mg iron/kg body weight (maximum 750 mg), average maximum total serum iron values of 310 µg/mL were measured after 1.12 hours. The terminal half-life was 9.8 hours, and the distribution volume

estimated by the population pharmacokinetic analysis was 0.42 to 3.14 l. Based on model-based simulations, the paediatrics subjects tended to have lower systemic exposure (lower $AUC_{0\text{-}72h}$) compared to the adults (median per age group: 3 340 µg×h/mL (1 to 2 years), 4 110 µg×h/mL (3 to 12 years), 4 740 µg×h/mL (13 to 17 years), 8 864 µg×h/mL (adults)).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeat dose toxicity and genotoxicity. Preclinical studies indicate that iron released from ferric carboxymaltose does cross the placental barrier and is excreted in milk in limited, controlled amounts. In reproductive toxicology studies using iron replete rabbits ferric carboxymaltose 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 ferric carboxymaltose. No evidence of allergic or immunotoxic potential has been observed. A controlled *in-vivo* test demonstrated no cross-reactivity of ferric carboxymaltose with anti-dextran antibodies. No local irritation or intolerance was observed after intravenous administration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid (pH adjustment)
Sodium hydroxide (pH adjustment)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Shelf life of the product as packaged for sale:
3 years

Shelf life after first opening of the container:
Chemical and physical in-use stability has been demonstrated for 7 days at 30°C.
From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, preparations for parenteral administration should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user. Administration of the product must be carried out under controlled and validated aseptic conditions.

Shelf life in polyethylene and polypropylene containers after dilution with sterile sodium chloride 9 mg/mL (0.9%)solution:
Chemical and physical in-use stability of the diluted product has been demonstrated for 72 hours at 30°C at concentrations of 2 mg/mL and 5 mg/mL.
From a microbiological point of view, the diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user, and would normally not be longer than 24 hours at 2 to 8°C, unless the dilution has taken place in controlled and validated aseptic conditions.

Shelf life in polypropylene syringe (undiluted):
Chemical and physical in-use stability has been demonstrated for 72 hours at 30°C.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and

would normally not be longer than 24 hours at 2 to 8°C, unless the transfer to the syringe has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 30 °C. Do not freeze.
For storage conditions after dilution or first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Fercarbos is supplied in a vial (type I glass) with a dark grey stopper (bromobutyl rubber) and aluminium seal as:

- 2 mL dispersion containing 100 mg iron. Available in pack sizes of 1, 2 or 5 vials.
- 10 mL dispersion containing 500 mg iron. Available in pack sizes of 1, 2 or 5 vials.
- 20 mL dispersion containing 1 000 mg iron. Available in a pack size of 1 vial.

Not all pack sizes may be marketed.

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 dispersion.

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

Fercarbos must only be mixed with sterile sodium chloride 9 mg/mL (0.9%) 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 related to equivalent iron dose, see section 4.2, Table 3.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}
Date of latest renewal: {DD month YYYY}

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

2026-07-08