

## Summary of Product Characteristics

### 1. Name of the medicinal product

FCM injection 50 mg iron/mL (ferric carboxymaltose)

### 2. Qualitative and quantitative composition.

Each 10 mL vial contains ferric carboxymaltose corresponding to 500 mg iron.

Excipient(s) with known effect

No excipients with known effect

For the full list of excipients, see section 6.1.

### 3. Pharmaceutical form

Solution for Injection/ Infusion Dark brown color solution

### 4. Clinical particulars

#### 4.1 Therapeutic indications

FCM 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

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

FCM 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 FCM administration (see section 4.4).

##### Posology

The posology of FCM follows a stepwise approach:

- Determination of the individual iron need,
- Calculation and administration of the iron dose(s), and
- Post-iron repletion assessments.

These steps are outlined below:

##### Step 1: Determination of the iron need

The individual iron need for repletion using FCM 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 section 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 FCM should be administered taking into consideration the following:

**Adults and adolescents aged 14 years and older**

A single FCM 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 FCM)

The maximum recommended cumulative dose of FCM is 1,000 mg of iron (20 mL FCM) 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 FCM administration should not exceed:

- 15 mg iron/kg body weight
- 750 mg of iron (15 mL FCM)

The maximum recommended cumulative dose of FCM is 750 mg of iron (15 mL FCM) 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 FCM 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 FCM has not been investigated in children below 1 year of age. FCM 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 FCM has not been investigated. FCM is therefore not recommended for use in children aged 1 to 13 years with chronic kidney disease requiring haemodialysis.

**Method of administration**

FCM 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.

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

#### *Intravenous injection*

FCM 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 FCM**

Volume of FCM 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*

FCM 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, FCM must only be diluted in sterile 0.9% m/V sodium chloride solution as shown in Table 3. Note: for stability reasons, FCM 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 FCM for intravenous infusion**

Volume of FCM 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 1,000 mg	250 mL	15 minutes

### **4.3 Contraindications**

The use of FCM is contraindicated in cases of:

- hypersensitivity to the active substance, to FCM or any of its 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).

FCM 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 FCM 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 1:1000 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 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 FCM 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 FCM. Paravenous leakage of FCM 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 FCM must be stopped immediately.

#### *Excipients*

FCM contains up to 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 FCM.

#### **4.6 Fertility, pregnancy and lactation**

##### **Pregnancy**

There are limited data from the use of FCM in pregnant women (see section 5.1). A careful benefit/risk evaluation is required before use during pregnancy and FCM 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 FCM 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 FCM can cross the placental barrier and that its use during pregnancy may influence skeletal development in the fetus (see section 5.3).

##### **Breast-feeding**

Clinical studies showed that transfer of iron from FCM to human milk was negligible ( $\leq 1\%$ ). Based on limited data on breast-feeding women it is unlikely that FCM represents a risk to the breast-fed child.

##### **Fertility**

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

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

FCM is unlikely to impair 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 FCM, 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**

<b>System Organ Class</b>	<b>Common (<math>\geq 1/100</math> to <math>&lt;1/10</math>)</b>	<b>Uncommon (<math>\geq 1/1,000</math> to <math>&lt;1/100</math>)</b>	<b>Rare (<math>\geq 1/10,000</math> to <math>&lt;1/1,000</math>)</b>	<b>Frequency not known<sup>(1)</sup></b>
<b>Immune system disorders</b>		Hypersensitivity	Anaphylactic reactions	
<b>Metabolism and nutritional disorders</b>	Hypophosphataemia			
<b>Nervous system disorders</b>	Headache, dizziness	Dysgeusia, paraesthesia		Loss of consciousness <sup>(1)</sup>
<b>Psychiatric disorders</b>			Anxiety <sup>(2)</sup>	
<b>Cardiac disorders</b>		Tachycardia		Kounis syndrome <sup>(1)</sup>
<b>Vascular disorders</b>	Flushing, hypertension	Hypotension	Presyncope <sup>(2)</sup> , syncope <sup>(2)</sup> , phlebitis	
<b>Respiratory, thoracic and mediastinal disorders</b>		Dyspnoea	Bronchospasm <sup>(2)</sup>	
<b>Gastrointestinal disorders</b>	Nausea	Abdominal pain, vomiting, constipation, diarrhoea, dyspepsia	Flatulence	
<b>Skin and subcutaneous tissue disorders</b>		Rash <sup>(3)</sup> , pruritus, urticaria, erythema	Angioedema <sup>(2)</sup> , distant skin discolouration <sup>(2)</sup> , pallor <sup>(2)</sup>	Face oedema <sup>(1)</sup>
<b>Musculoskeletal and connective tissue disorders</b>		Arthralgia, myalgia, pain in extremity, back pain, muscle spasms		Hypophosphataemic osteomalacia <sup>(1)</sup>
<b>General disorders and administration site conditions</b>	Injection/infusion site reactions <sup>(4)</sup>	Pyrexia, fatigue, chills, chest pain, oedema peripheral, malaise	Influenza like illness (whose onset may vary from a few hours to several days) <sup>(2)</sup>	
<b>Investigations</b>		Alanine aminotransferase increased,		

		aspartate aminotransferase increased, gamma- glutamyltransferase increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased		
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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).

### **Paediatric population**

The safety profile for children and adolescents aged 1 to 17 years is comparable with that of adults. 110 paediatric patients received FCM 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: pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) <https://pv.pharmacyboardkenya.org>.

### **4.9 Overdose**

Administration of FCM 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

FCM 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 <sup>59</sup>Fe from radio-labelled FCM 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.

FCM 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 FCM 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 FCM (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 FCM 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 FCM (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 FCM 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 FCM (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 FCM 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 FCM (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 FCM vs. standard of care was demonstrated with the primary efficacy endpoint, the change in weight-adjusted peak VO<sub>2</sub> 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 FCM (n=97) to iron sucrose (n=86) in subjects with ID anaemia undergoing haemodialysis. Subjects received FCM 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 FCM: 1,700 mg). The primary efficacy endpoint was the percentage of subjects reaching an increase in Hb of  $\geq 1.0$  g/dL at 4 weeks after baseline. At 4 weeks after baseline, 44.1% responded to treatment with FCM (i.e. Hb increase of  $\geq 1.0$  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 FCM ( $n=147$ ) vs. oral iron ( $n=103$ ). Subjects in the FCM 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  $\geq 1.0$  g/dL anytime between baseline and end of study or time of intervention. This was achieved by 60.54% of subjects receiving FCM 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 FCM 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 FCM vs. oral ferrous sulphate in reducing ID anaemia in subjects with inflammatory bowel disease (IBD). Subjects received either FCM ( $n=111$ ) 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 FCM 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 FCM vs. iron sucrose in subjects with remitting or mild IBD. Subjects receiving FCM 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 FCM ( $n=240$ ; 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  $\geq 2$  g/dL). 83.8% of FCM-treated subjects vs. 75.9% of iron sucrose-treated subjects achieved a Hb increase  $\geq 2$  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 FCM ( $n=227$ ) vs. ferrous sulphate ( $n=117$ ) in women suffering from post-partum anaemia. Subjects received either FCM

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 FCM 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 FCM 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 FCM (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 FCM 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 FCM treated women and those treated with oral iron (11.4% FCM 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, coeliac 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 FCM 7.5 mg iron/kg body weight (n = 16) or FCM 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 FCM 7.5 mg iron/kg and 2.8 (1.15) g/dL with FCM 15 mg iron/kg. See also section 4.8.

In a prospective, open-label, parallel-group phase 3 study (1VIT17044), efficacy and safety of FCM 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 FCM 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 FCM 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 FCM 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 FCM 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 FCM 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 <sup>59</sup>Fe and <sup>52</sup>Fe from FCM 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 FCM 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 FCM 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 FCM 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 paediatric subjects tended to have lower systemic exposure (lower AUC<sub>0-72h</sub>) 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**

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 FCM does cross the placental barrier and is excreted in milk in limited, controlled amounts. In reproductive toxicology studies using iron replete rabbits FCM was associated with minor skeletal abnormalities in the fetus. 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 FCM. No evidence of allergic or immunotoxic potential has been observed. A controlled in-vivo test demonstrated no cross-reactivity of FCM with anti-dextran antibodies. No local irritation or intolerance was observed after intravenous administration.

## **6. Pharmaceutical particulars**

### **6.1 List of excipients**

Water for injections

### **6.2 Incompatibilities**

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

The compatibility with containers other than polypropylene, polyethylene and glass is not known.

### **6.3 Shelf life**

*Shelf life of the product as packaged for sale:*

2 years.

*Shelf life after first opening of the container:*

From a microbiological point of view, 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.

Chemical and physical in-use stability has been demonstrated for 7 days at 30° C.

*Shelf life in polyethylene and polypropylene containers 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.

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.

Chemical and physical in-use stability has been demonstrated for 72 hours at 30° C at concentrations of 2 mg/ml and 5 mg/ml.

*Shelf life in polypropylene syringe (undiluted):*

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.

Chemical and physical in-use stability has been demonstrated for 72 hours at 30° C.

#### **6.4 Special precautions for storage**

Store in the original package in order to protect from light. 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**

FCM is supplied in a vial (type I glass) with a stopper (bromobutyl rubber) and an aluminium cap containing:

#### **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.

For storage conditions after dilution or first opening of the medicinal product, see section 6.3.

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

FCM 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. Marketing authorisation holder**

Genix Pharma (Private) Limited,  
44-45-B, Korangi Creek Road, Karachi-75190, Pakistan

#### **Manufacturing address.**

Genix pharma  
44-45 b, korangi creek road, karachi-75190, pakistan

### **8. Marketing authorisation number(s)**

H2024/CTD10413/23937

### **9. Date of first authorisation/renewal of the authorisation**

Date of first authorisation: 09/02/2024.

### **10. Date of revision of the text**

November 2024.