Ferium
(Ferric Carboxymaltose)
Injection

فیریئم
(فیرک کاربوکسی مالٹوز)
انجیکشن

500mg/10mL

Solution for Injection/Infusion 4000003140A

Composition:
Each 10mL Vial contains:
Ferric Carboxymaltose eq. to Elemental Iron .....500mg.

DESCRIPTION
Pharmaceutical Form: Solution for Injection/Infusion
Proper Name: Ferric Carboxymaltose.
Chemical Name: Polynuclear iron (III)-hydroxide 4(R)-(poly-(1→4)-O-α-Dglucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate.
Molecular Formula and Molecular Weight: $C_{24}H_{44}FeO_{25}$ and 788.4 g/mol

CLINICAL PARTICULARS
Therapeutic indications:
Ferium(Ferric carboxymaltose) is indicated for the treatment of iron deficiency when:
- 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.

Posology and method of administration
Monitor carefully patients for signs and symptoms of hypersensitivity reactions during and following each administration of **Ferium**(Ferric carboxymaltose).
Ferium(Ferric carboxymaltose) 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 **Ferium**(Ferric carboxymaltose) administration.

Posology
The posology of **Ferium**(Ferric carboxymaltose) follows a stepwise approach:
- Determination of the individual iron need
- Calculation and administration of the iron dose(s)
- Post-iron repletion assessments.

These steps are outlined below:

Step 1: Determination of the iron need:
The individual iron need for repletion using **Ferium**(Ferric carboxymaltose) 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.
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 **Ferium**(Ferric carboxymaltose) should be administered taking into consideration the following:
Adults and adolescents aged 14 years and older:
A single **Ferium**(Ferric carboxymaltose) 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)
- The maximum recommended cumulative dose of **Ferium**(Ferric carboxymaltose) is 1,000 mg of iron 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 **Ferium**(Ferric carboxymaltose) administration should not exceed:
- 15 mg iron/kg body weight 750 mg of iron
- The maximum recommended cumulative dose of **Ferium**(Ferric carboxymaltose) is 750 mg of iron 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 **Ferium**(Ferric carboxymaltose) 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 **Ferium**(Ferric carboxymaltose) has not been investigated in children below 1 year of age. **Ferium**(Ferric carboxymaltose) 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. In children aged 1 to 13 years with chronic kidney disease requiring haemodialysis, the efficacy and safety of **Ferium**(Ferric carboxymaltose) has not been investigated.**Ferium**(Ferric carboxymaltose) is therefore not recommended for use in children aged 1 to 13 years with chronic kidney disease requiring haemodialysis.
Method of administration **Ferium**(Ferric carboxymaltose) must only be administered by the intravenous route:
- By injection, or by infusion
- During a haemodialysis session undiluted directly into the venous limb of the dialyser.

Ferium(Ferric carboxymaltose) must not be administered by the subcutaneous or intramuscular route.
Intravenous injection **Ferium**(Ferric carboxymaltose) 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 Ferium(Ferric carboxymaltose)

Volume of **Ferium** (Ferric carboxymaltose) 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
- **Ferium**(Ferric carboxymaltose) 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, **Ferium**(Ferric carboxymaltose) must only be diluted in sterile 0.9% m/V sodium chloride solution as shown in Table 3. No other intravenous dilution solutions and therapeutic agents should be used, as there is the potential for precipitation or interaction.
- **Note**: for stability reasons, **Ferium**(Ferric carboxymaltose) should not be diluted to concentrations less than 2 mg iron/mL (not including the volume of the ferric carboxymaltose dispersion).

Table 3: Dilution plan of Ferium(Ferric carboxymaltose) for intravenous infusion

Volume of **Ferium** (Ferric carboxymaltose) 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

Shelf life and other instructions:
The product will have a shelf life of two 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.

Other instructions:
Inspect vials visually for sediment and damage before use. Use only those containing sediment-free, homogeneous dispersion.
Each vial of **Ferium**(Ferric carboxymaltose) is intended for single use only.Any unused product or waste material should be disposed of in accordance with local requirements.

Contraindication
- Hypersensitivity to the active substance, to Ferric carboxymaltose or any of excipients.
- 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.

WARNINGS AND PRECAUTIONS
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. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately.

Hypophosphataemic osteomalacia Ferric carboxymaltose treatment may be repeated if IDA reoccurs. Check serum phosphate levels in patients at risk for low serum phosphate who require a repeat course of treatment or for any patient who receives a repeat course of treatment within three months.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 Ferric carboxymaltose 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 Ferric carboxymaltose must be stopped immediately.

Hypertension In clinical studies, hypertension was reported in 4% (67/1,775) of subjects in clinical trials 1 and 2. Transient elevations in systolic blood pressure, sometimes occurring with facial flushing, dizziness, or nausea were observed in 6% (106/1,775) of subjects in these two clinical trials. These elevations generally occurred immediately after dosing and resolved within 30 minutes. Monitor patients for signs and symptoms of hypertension following each Ferric carboxymaltose administration.

Laboratory Test Alterations In the 24 hours following administration of Ferric carboxymaltose, laboratory assays may overestimate serum iron and transferrin bound iron by also measuring the iron in Ferric carboxymaltose.

USE IN SPECIFIC POPULATIONS

Pregnancy There are limited data from the use of Ferric carboxymaltose in pregnant women. A careful benefit/risk evaluation is required before use during pregnancy and Ferric carboxymaltose 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 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. 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 Ferric carboxymaltose can cross the placental barrier and that its use during pregnancy may influence skeletal development in the fetus.

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.

Geriatric Use Of the 1,775 subjects in clinical studies of Ferric carboxymaltose, 50% were 65 years and over, while 25% were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Drug Interactions

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 Ferric carboxymaltose.

Adverse Reactions

The most commonly reported ADR is nausea followed by injection/infusion site reactions, hypophosphataemia, headache, flushing, dizziness and hypertension. The most serious ADR is anaphylactic reactions (rare); fatalities have been reported.

Adverse drug reactions observed during clinical trials and post-marketing Experience:

Common (≥1/100 to <1/10): Hypophosphataemia, Headache, dizziness, Flushing, Hypertension, Nausea, Injection/infusion site Reactions.

Uncommon (≥1/1,000 to <1/100): Hypersensitivity, Dysgeusia, Paraesthesia, Tachycardia, Hypotension, Dyspnoea, Abdominal pain, vomiting, constipation, diarrhoea, dyspepsia, Rash, pruritus, urticaria, erythema, Arthralgia, myalgia, pain in extremity, back pain, muscle spasms, Pyrexia, fatigue, chills, chest pain, oedema peripheral, malaise, Alanine aminotransferase increased, aspartate aminotransferase increased, gammaglutamyltransferase increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased.

Rare (≥1/10,000 to <1/1,000): Anaphylactic reactions, Anxiety, Presyncope, syncope, phlebitis, Bronchospasm, Flatulence, Angioedema, distant skin discolouration, pallor, Influenza like illness (whose onset may vary from a few hours to several days).

Frequency not Known: Loss of Consciousness, Kounis syndrome, Face oedema, Hypophosphataemic Osteomalacia.

Others: Platelet count decreased, White blood cell count decreased.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system @ https://ferozsons-labs.com/drug-safety-2/

By reporting side affects you can help provide more information on the safety of this medicine.

Effects on ability to drive and use machines

Ferric carboxymaltose is unlikely to impair the ability to drive and use machines.

OVERDOSAGE

Administration of Ferric carboxymaltose 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.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Pharmacotherapeutic group: Iron trivalent, parenteral preparation. Ferric carboxymaltose 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-labelled 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.

Pharmacokinetics

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.

Carcinogenesis, mutagenesis and impairment of fertility

Carcinogenicity studies have not been performed with ferric carboxymaltose. Ferric carboxymaltose was not genotoxic in the animal genetic toxicology studies.

Fertility There are no data on the effect of Ferric carboxymaltose on human fertility. Fertility was unaffected following Ferric carboxymaltose treatment in animal studies.

HOW SUPPLIED

Each pack contains one vial of **Ferium** (Ferric Carboxymaltose) solution for injection/infusion enclosed in a PVC Tray.

STORAGE

Store at 20°C to 25°C.

INSTRUCTIONS

Do not freeze.Before using check on the absence of sediments.Protect from Heat and Light. Keep out of reach of Children.To be sold on the prescription of registered medical practitioner only.

Please read the contents cautiously before use.
This package insert is regularly and timely updated.

Manufactured by:

BF BIOSCIENCES

FEROZSONS LABORATORIES LIMITED

BF BIOSCIENCES LIMITED

(A Subsidiary of FEROZSONS LABORATORIES LIMITED)

5-KM, Sundar Raiwind Road, Raiwind, Lahore, Pakistan.

Mfg.Lic.No: 000655