FERRLECIT-V-21.0

1. NAME OF THE MEDICINAL PRODUCT

Ferrlecit

Active substance: Iron as sodium ferric gluconate complex 62.5 mg/5ml

Solution for injection or concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ampoule of 5 ml contains:
Sodium ferric gluconate complex equivalent to: 62.5 mg iron (III) ion,
manufactured from:
Sodium carbonate decahydrate
Ferric chloride hexahydrate
Sodium gluconate
Sodium carbonate, anhydrous
Water for injection

Excipients with known effect:
Contains 45 mg benzyl alcohol per ampoule (5 ml), equivalent to 9 mg/ml,
975 mg of sucrose per 5 ml ampoule
(see sections 4.3, 4.4 and 4.8).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection or concentrate for solution for infusion.
Clear, dark brown solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ferrlecit is indicated in adults and children from 6 years and above.
Severe iron deficiency states only when oral administration has been found impossible; in cases of gastrointestinal malabsorption which rules out oral iron therapy; patients treated by dialysis getting erythropoietin.

4.2 Posology and method of administration

Unless otherwise ordered, depending on the degree of iron deficiency, adults are given one ampoule daily of 5 ml by infusion after dilution with physiological saline solution or by slow intravenous injection.
Not more than one ampoule should be given, even in exceptional cases such as marked iron deficiency after repeated autologous blood donation.
For preference, the product can be given as an intravenous infusion over 20 to 30 minutes, diluted with 100 to 250 ml of physiological saline solution.
I.V. injections must always be given very slowly with the patient supine.

Monitor carefully patients for signs and symptoms of hypersensitivity reactions during and following each administration of Ferrlecit.
Ferrlecit 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 Ferrlecit injection (see section 4.4).

Patients with impaired hepatic or renal function
Ferrlecit is contraindicated in patients with severe inflammatory diseases of the liver or kidneys (see section 4.3).

Paediatric population

Due to lack of clinical data on safety and efficacy, Ferrlecit solution for injection or concentrate for solution for infusion is contraindicated in children younger than the age of 6 years.

From six years upwards until achievement of a body weight of 40 kg, children with iron deficiency and erythropoietin therapy under haemodialysis receive a dose of 0.12 ml Ferrlecit/kg body weight, equivalent to 1.5 mg iron (III) ion/kg body weight at each dialysis.
Children and adolescents with a body weight of more than 40 kg receive a single dose of 5 ml Ferrlecit, equivalent to 62.5 mg iron (III) ion at each dialysis.
The duration of treatment depends on the degree of iron deficiency, that can be approximately calculated according to the following equation:

Required amount of iron [mg] = body weight [kg][1)] x Hb deficit [g/dl][2)] x factor 3.5

[1)] to be based on the normal weight in the case of overweight patients.

[2)] target Hb corresponding to normal for age and gender.

Reliable values for serum ferritin and transferrin saturation will not be obtained for at least one week after the last Ferrlecit dose. Total and reticulocyte haemoglobin begin to increase within one to two weeks of starting treatment.

4.3 Contraindications

You must not receive Ferrlecit in case of

- hypersensitivity to the active substance, to Ferrlecit or to any of the excipients listed in section 6.1.
- severe known hypersensitivity to other parenteral iron preparations,
- hypersensitivity to benzyl alcohol,
- iron accumulation (haemochromatosis, chronic haemolysis) or problems assimilating iron (sideroblastic anaemia, lead-induced anaemia, thalassaemia),
- severe inflammatory renal or hepatic disorders,
- premature infants, newborns, infants and small children up to 6 years of age (see also section 4.4).
- Because of its sucrose content, this medicinal product must not be used in patients suffering from hereditary fructose intolerance.

4.4 Special warnings and precautions for use

Parenterally administered iron preparations may cause hypersensitivity reactions, including serious and potentially fatal anaphylactic/anaphylactoid reactions. Hypersensitivity reactions have also been reported after previous, uncomplicated, tolerated injections of parenteral iron preparations. There are reports of hypersensitivity reactions that have developed into Kounis syndrome (acute allergic coronary artery spasms that can lead to myocardial infarction, see section 4.8).

The risk is increased in patients with known allergies, including drug allergies, as well as in those with a history of severe asthma, eczema or other atopic allergy.
In patients with immunological or inflammatory diseases (e.g. systemic lupus erythematosus, rheumatoid arthritis, Crohn's disease), there is also an increased risk of hypersensitivity reactions in the parenteral administration of iron complex preparations.

Ferrlecit should only be used if trained specialists in the detection and treatment of anaphylactic reactions are immediately available and if cardiopulmonary resuscitation is ensured by appropriate equipment. Each patient should be observed for the occurrence of undesirable effects for at least 30 minutes after each Ferrlecit injection. If hypersensitivity reactions or signs of intolerance occur during treatment, treatment must be discontinued immediately. Equipment for cardiopulmonary resuscitation and for the treatment of an acute anaphylactic/anaphylactoid reaction should be available, including an injectable 1:1,000 adrenaline solution. If necessary, additional treatment with antihistamines and/or corticosteroids should be administered.

The degree of iron deficiency must imperatively be assessed prior to IV administration in order to prevent haemosiderosis.

As this medicine contains benzyl alcohol, accidental injection outside of the vein and intramuscular injection are painful and should therefore be avoided. In addition, accidental paravasal use can cause reddish-brown discolouration of the skin.

Benzyl alcohol can cause toxic and anaphylactoid reactions in infants and children under 3 years of age.
The use of medicinal products containing benzyl alcohol has been associated with fatal gasping syndrome in premature infants, newborns and young children (symptoms: sudden onset of gasping, drop in blood pressure, bradycardia and cardiovascular collapse).
Since benzyl alcohol can cross the placental barrier, the solution for injection or the concentrate for solution for infusion should only be used with caution during pregnancy (see section 4.6).

Large amounts of benzyl alcohol should only be used with caution and when absolutely necessary due to the risk of accumulation and toxicity (metabolic acidosis), especially in persons with impaired liver or kidney function and during pregnancy and lactation.

Ferrlecit contains less than 1 mmol sodium (23 mg) per ampoule, that is to say it is essentially "sodium-free".

Ferrlecit should not be used in patients with the rare hereditary fructose intolerance.

4.5 Interaction with other medicinal products and other forms of interaction

If Ferrlecit is used in patients receiving treatment with ACE inhibitors, the frequency and severity of possible anaphylactic/anaphylactoid reactions to Ferrlecit treatment may be increased.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate and controlled studies on the use of Ferrlecit in pregnant women. A careful risk-benefit assessment is therefore required before use during pregnancy, and Ferrlecit should not be used during pregnancy unless clearly necessary (see section 4.4).

Iron deficiency anaemia occurring in the first trimester of pregnancy can in many cases be treated with orally administered iron preparations. Treatment with Ferrlecit should be limited to the second and third trimesters if the benefit of the therapy is assessed to be greater than the potential risk to the mother and foetus.

Animal experimental studies have shown reproduction toxicity (see section 5.3). The potential risk to humans is not known.

Foetal bradycardia may occur after parenteral iron administration. This is usually temporary and occurs as a result of a hypersensitivity reaction of the mother.

Because of the rare circulatory reaction that can be caused by iron injection, there is a potential risk in pregnant women (see section 4.8) that, due to insufficient blood flow to the placenta, nutrition disorders may occur in the unborn child. Special attention must therefore be paid to correct use (see section 4.2).

Breast-feeding
It is not known whether increased excretion of iron into breast milk takes place after parenteral administration of iron. Ferrlecit should therefore only be used during breast-feeding after a careful risk-benefit assessment.

Fertility
There are no studies on the effect of Ferrlecit on fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The following categories are used to express the frequency of undesirable effects:

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)
not known	(cannot be estimated from the available data)

Immune system disorders
Rare: Anaphylactic reactions including oedema of various parts of the body (angio-oedema), including the face, mouth and throat area (e.g. swelling of the glottis), anaphylactoid reactions and anaphylactic shock.
Not known: Hypersensitivity reactions (usually fever and/or arthralgia and/or nausea/vomiting).

Blood and lymphatic system disorders:
Very rare: Haemolysis, haemoglobinuria (in case of overload of the transferrin system).

Nervous system disorders
Not known: Generalised seizure, headache.

Cardiac disorders
Not known: Kounis syndrome, palpitations, tachycardia, foetal bradycardia (see section 4.6).

Vascular disorders
Rare: Drop in blood pressure even progressing to circulatory failure.
Not known: Superficial thrombophlebitis at the injection site.

Respiratory, thoracic and mediastinal disorders
Rare: Pulmonary oedema, swelling of the bronchial mucosa with respiratory problems.

Gastrointestinal disorders:
Not known: Diarrhoea.

Skin and subcutaneous tissue disorders
Rare: Exanthematous skin changes.

General disorders and administration site conditions
Not known: Flu-like symptoms that can occur within a few hours or several days.

Additional undesirable effects with intravenous injection
Additional undesirable effects reported with intravenous use are listed below. Therefore, the IV injection should always be given very slowly with the patient in supine position.
The frequency of these undesirable effects could not be estimated from the available data.

Nervous system disorders
Paraesthesia, light-headedness, taste disorders.

Gastrointestinal disorders
Nausea, abdominal pain, vomiting.

Skin and subcutaneous tissue disorders
Erythema of the face.

Musculoskeletal and connective tissue disorders
Pain in the chest and back, muscle and joint pain, especially in the presence of rheumatism.

Vascular disorders
Blood pressure increase.

Use in children
In a clinical study of dialysis-dependent children, the following events were observed:

Cardiac disorders
Very common: Heart palpitations.

Infections and infestations
Common: Infections, pharyngitis, sinusitis.

Vascular disorders
Very common: Increased blood pressure, decreased blood pressure.
Common: Thrombosis.

Gastrointestinal disorders
Very common: Nausea, vomiting, abdominal pain.

Musculoskeletal and connective tissue disorders
Common: Muscle and joint pain, chest and back pain.

General disorders and administration site conditions
Very common: Headaches.
Common: Fever, swelling of the face.

Benzyl alcohol can cause allergic reactions.

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 to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il/

4.9 Overdose

Signs of Ferrlecit overdose can include diarrhoea, circulatory collapse, shock, pallor, respiratory distress, restlessness, giddiness and coma. Fever and seizures have also been reported.

A Ferrlecit overdose can lead to an accumulation of iron in the iron storage pools and potentially to haemosiderosis. Treatment and appropriate supportive therapy must be provided as soon as possible.

If iron overload is detected/confirmed by lab tests, a chelating agent such as deferoxamine may be considered. If blood iron levels exceed 3 mg/l and the iron binding capacity of transferrin is exceeded, IV infusion of 1 to 2 g deferoxamine (16 mg/kg/hour maximum) is recommended. If necessary, the infusion should be repeated the next day and serum iron values should be checked.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Iron-containing preparations,
ATC code: B03AC.

In the event of iron loss or increased iron requirements in the organism, the iron content in Ferrlecit substitutes the lack of iron. Thus, a sufficient quantity of iron can be provided to the erythropoietic centres for haemoglobin formation. The formation of physiological iron reserves is also possible.

The efficacy of iron replacement is initially expressed by an increase in the reticulocyte count as well as an increase in the haemoglobin value, the haemoglobin concentration/single erythrocyte count and an increase in the red blood cell count.

5.2 Pharmacokinetic properties

Sodium ferric gluconate complex enters the liver via the blood. There, after enzymatic splitting and release of the iron, the trivalent iron binds to transferrin, the carrier protein for plasma iron, which takes over the transport to the erythropoiesis centres and the depots. If no pathological iron loss occurs due to bleeding, the iron content of the organism is – almost completely preserved, – apart from minimal physiological daily iron elimination.

5.3 Preclinical safety data

Preclinical data on safety pharmacology and toxicity with single or repeated administration did not reveal any information that is not already mentioned in other points of the Summary of Product Characteristics.
There is no evidence of a potential mutagenicity of iron in mammalian cells *in vivo*. There are no long-term studies on tumorigenic potential.

Animal studies in rats and mice showed no evidence of teratogenic effects, but embryotoxic and foetotoxic effects occurred at doses far above the human therapeutic dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose, benzyl alcohol, water for injection.

6.2 Incompatibilities

Under no circumstances should the medicine be mixed with another medicine in the same syringe.

Reducing substances (e.g. vitamin C, rutin, glucose, cysteine and other substances containing SH groups) must not be administered concomitantly with Ferrlecit intravenously.

6.3 Shelf life

The expiry date of this product is indicated on the packaging materials.

6.4 Special precautions for storage

Store at **a temperature not exceeding** 25°C in **the original package, in** order to protect from light.

The **prepared infusion** solution can be stored **for 24 hours** at room temperature**.**

6.5 Nature and contents of container

Pack of 5 ampoules of 5 ml.

6.6 Special precautions for disposal

No special requirements.

7. LICENSE HOLDER AND IMPORTER AND ITS ADDRESS

sanofi-aventis Israel ltd, 10 Beni Gaon St., Netanya 4250499.

Revised in September 2023 according to MoH guidelines.