1. NAME OF THE MEDICINAL PRODUCT

Ferrlecit

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ampoule of 5 ml contains:
Sodium ferric gluconate complex equivalent to: 62.5 mg iron (III) ion,

prepared 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 a 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

Ferrlecit may not be used in

- hypersensitivity to the active substance, to Ferrlecit or any of its excipients listed in section 6.1.
- known serious hypersensitivity to other parenteral iron products,
- hypersensitivity to benzyl alcohol,
- iron overload (haemochromatosis, chronic haemolysis) or iron utilisation disorders (sideroblastic anaemia, lead anaemia, thalassaemia),
- severe inflammatory diseases of the liver or kidneys,
- premature babies, neonates, infants and small children up to6 years of age.

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 can cause hypersensitivity reactions including serious and potentially fatal anaphylactic/anaphylactoid 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, Crohn's disease).

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. Each patient should be observed for adverse effects for at least 30 minutes following each Ferrlecit injection. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. Facilities for cardiorespiratory resuscitation and equipment for handling acute anaphylactic/anaphylactoid reactions should be available, including an injectable 1:1000 adrenaline solution. Additional treatment with antihistamines and/or corticosteroids should be given as appropriate.

In order to avoid haemosiderosis, it is essential to calculate the amount of iron required before the i.v. administration of iron.

Accidental paravenous or intramuscular injection is painful due to the content of benzyl alcohol and must therefore be avoided. In addition, accidental paravenous administration can lead to reddish-brown discolouration of the skin.

Benzyl alcohol may cause toxic and anaphylactoid reactions in infants and children up to 3 years old.

The administration of medications containing benzyl alcohol to newborns or premature neonates and small children has been associated with a fatal "Gasping Syndrome" (symptoms include a striking onset of gasping syndrome, hypotension, bradycardia, and cardiovascular collapse).

As benzyl alcohol may cross the placenta, solution for injection should only be used with caution in pregnancy (see also section 4.6).

High amounts of benzyl alcohol should only be used with caution and if absolutely necessary, especially in subjects with liver or kidney impairment and during pregnancy and lactation because of the risk of accumulation and toxicity (metabolic acidosis).

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

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

4.5 Interactions with other medicinal products and other forms of interaction

The incidence and severity of possible anaphylactic/anaphylactoid reactions with Ferrlecit therapy can be increased if Ferrlecit is used in patients under treatment with ACE-inhibitors.

4.6 Fertility, Pregnancy and lactation

Pregnancy

There are no adequate and well-controlled trials of Ferrlecit in pregnant women. A careful risk/benefit evaluation 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 oral iron. Treatment with Ferrlecit should be confined to second and third trimester if the benefit is judged to outweigh the potential risk for both the mother and the foetus.

Animal studies have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Foetal bradycardia may occur following administration of parenteral irons. It is usually transient and a consequence of a hypersensitivity reaction in the mother.

Due to the rarely occurring circulatory reactions that an injection of iron can cause (see section 4.8), there is the potential risk with pregnant women that nutritional disorders occur in the foetus due to inadequate blood supply to the placenta. Therefore, particular attention should be paid to correct use (see section 4.2).

Breast-feeding
It is not known whether excretion of iron into breast milk is increased after parenteral administration of iron. Ferrlecit should therefore be used during lactation only after a careful weighing up of the benefits and risks.

Fertility
Studies to assess the effect of Ferrlecit on fertility were not conducted.

4.7 Effects on ability to drive and use machines

No studies of the effects on the ability to drive or operate machines have been undertaken.

4.8 Undesirable effects

The frequencies of undesirable effects are based on the following categories:

Very common	(≥ 1/10)
Common	(≥ 1/100, < 1/10)
Uncommon	(≥ 1/1,000, < 1/100)
Rare	(≥ 1/10,000, < 1/1,000)
Very rare	(< 1/10,000)
Not known	(frequency cannot be estimated on the basis of the available data)

Immune system disorders
Rare: anaphylactic reactions including oedema in various parts of the body (angioedema), also in the area of the face, mouth and throat (e.g. oedema glottidis), anaphylactoid reactions and anaphylactic shock

Not known: hypersensitivity-like reactions (mostly fever and/or arthralgia and/or nausea/vomiting).

Blood and lymphatic system disorders
Very rare: haemolysis, haemoglobulinuria (on overload of the transferrin system)

Nervous system disorders
Not known: generalized seizures, headache

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

Vascular disorders
Rare: hypotensive events even progressing to circulatory collapse
Not known: superficial thrombophlebitis at injection site

Respiratory, thoracic and mediastinal disorders
Rare: pulmonary oedema, swelling of the bronchial mucosa with dyspnoea

Skin and subcutaneous tissue disorders
Rare: exanthematous skin changes

General disorders and administration site conditions
Not known: influenza like illness whose onset may vary from a few hours to several days

Additional undesirable effects upon intravenous injection

Additional undesirable effects that have been reported on intravenous injection are listed below. Therefore, the i.v. injection should always be given very slowly, with the patient supine.

The frequency of these undesirable effects cannot be estimated from the available data.

Nervous system disorders
Paraesthesia, dizziness, taste disorders

Gastrointestinal disorders
Nausea, abdominal pains, vomiting

Skin and subcutaneous tissue disorders
Facial erythema. *Musculoskeletal and connective tissue disorders*
Pain in the chest and back, muscle and joint pain, especially in patients with rheumatic disorders

Vascular disorders
Hypertension

Use in children

The following events were observed in a clinical study in dialysis-dependent children:

Cardiac disorders
Very common: palpitations

Infections and infestations
Common: infections, pharyngitis, sinusitis

Vascular disorders
Very common: hypertension, hypotension
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: headache
Common: fever, facial oedema

Benzyl alcohol may 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 an overdose with Ferrlecit may be circulatory collapse, shock, pallor, dyspnoea, restlessness as well as drowsinessand coma. Fever and convulsions have also been reported.

An overdose of Ferrlecit can lead to accumulation of iron in iron stores and potentially lead to haemosiderosis.
Treatment and appropriate supportive therapy must be given as soon as possible.

If iron overload is detected / confirmed by laboratory testing, 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 (maximum 16 mg/kg/hour) is recommended. If necessary, the infusion should be repeated the next day and the serum iron levels should be checked.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: iron-containing preparations, ATC code: B03A C07

If the body suffers iron loss or its iron requirements are increased, the iron deficit is replaced by the iron contained in Ferrlecit. This provides the erythropoietic centres with adequate amounts of iron for the formation of haemoglobin. Likewise, it enables physiological iron reserves to be built up.

The effectiveness of iron replacement is reflected first in an increase in numbers of reticulocytes as well as a rise in haemoglobin level, haemoglobin concentration per single erythrocyte and an increase in numbers of erythrocytes.

5.2 Pharmacokinetic properties

Sodium ferric gluconate complex reaches the liver via the blood. In the liver, the trivalent iron released after enzymatic cleavage is bound to transferrin, the carrier protein for iron in plasma, which takes over the transport to centres of erythropoiesis and the depots. If there is no pathological loss of iron through bleeding, the iron stores of the body – apart from a minimal physiological daily elimination of iron - remain virtually intact.

5.3 Preclinical safety data

Preclinical data concerning safety pharmacology and toxicity on single or repeated administration produced no information that is not already mentioned in other sections of the SPC.

There is no evidence of a potential mutagenicity of iron in mammalian cells *in vivo*. No long-term studies on carcinogenic potential are available.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose, benzyl alcohol, water for injection.

6.2 Incompatibilities

Not to be mixed in syringes with other drugs!

Reducing substances (e.g., vitamin C, rutin, glucose, cysteine and other substances containing SH-groups) must not be administered at the same time as Ferrlecit solution for injection i.v.

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 July 2022 according to MoH guidelines.