יוני 2014

Ferrlecit solution for injection

חומר פעיל: Iron as sodium ferric gluconate complex 62.5 mg/5ml

חברת סאנופי אוונטיס מבקשת להודיע על עדכון העלון לרופא שאושר ביוני 2014.

לתשומת ליבכם, העדכון כולל בין השאר עדכון של ההתוויה להגבלת השימוש מגיל 6 שנים.

ההתוויה הקודמת:

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.

ההתוויה החדשה:

Ferrlecit is indicated in adults and children 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.

העלון בו מסומנים העדכונים מצורף להודעה זו.

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מצ"ב בנוסף מכתב לצוות הרפואי בנושא:

Strengthened recommendations regarding the risk of serious hypersensitivity reactions with intravenous iron products

העלון המעודכן נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות וניתן לקבלו מודפס על ידי פנייה לבעל הרישום , סאנופי-אוונטיס ישראל בע"מ, רח' בני גאון 10 נתניה או בטלפון : 09-8633700 .

מצורף הקישור לאתר משרד הבריאות.

http://www.old.health.gov.il/pages/default.asp?maincat=11&catid=38&pageid=165

בברכה,

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Strengthened recommendations regarding the risk of serious hypersensitivity reactions with intravenous iron products

Dear healthcare professional,

Important information regarding intravenous (IV) iron products has arisen from a European review of their benefits versus risks following concerns about the risk of serious hypersensitivity reactions.

Summary

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 (including a negative test dose, see below). The benefits of IV iron products in the iron deficiency situations where the oral iron is not sufficient or tolerated continue to outweigh the risks based on the current available data provided that the following recommendations are followed:

- **IV iron products should not be used in patients with hypersensitivity to the active substance, the product itself, or any of its excipients; and in patients with serious hypersensitivity to other parenteral iron products.**
- **Hypersensitivity reactions have also been reported after previously uneventful doses of parenteral iron complexes.**
- **The risk of hypersensitivity is increased in patients with known allergies (including drug allergies) and in patients with immune or inflammatory conditions (e.g. systemic lupus erythematosus, rheumatoid arthritis) as well as in patients with a history of severe asthma, eczema or other atopic allergy.**
- **IV iron products should only be administered when staff trained to evaluate and manage anaphylactic/anaphylactoid reactions as well as resuscitation facilities are immediately available.**
- **Each patient should be observed for adverse effects for at least 30 minutes following each IV iron product injection. 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/anaphylactoid reactions should be available, including an injectable 1:1000 adrenaline solution. Additional treatment with antihistamines and/or corticosteroids should be given as appropriate.**
- **All prescribers should inform patients of the risk of hypersensitivity before each administration. Patients should be informed of the relevant symptoms and asked to seek urgent medical attention if a reaction occurs.**
- **IV iron products should not be used during pregnancy unless clearly necessary. Treatment should be confined to 2nd or 3rd trimester, if the benefit is clearly judged to outweigh the potential risks for both the mother and the foetus. The risks to the foetus can be serious and include foetal anoxia and distress.**

Further information

IV iron products are indicated in iron-deficiency situations when the oral route is insufficient or poorly tolerated. The diagnosis must be based on appropriate laboratory tests.

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The safety concern

A European review was initiated due to safety concerns regarding the risk of serious hypersensitivity reactions, including when used during pregnancy. All IV iron products can cause serious hypersensitivity reactions, **these may occur even when a previous administration has been tolerated (including a negative test dose). Fatal outcomes have been observed.**

Product information about the risk of hypersensitivity reactions has been reviewed and strengthened, and is now consistent for all IV iron products. Changes to the product information specific to hypersensitivity reactions are highlighted in the annex of this letter. These measures are intended to heighten awareness of the risk of serious hypersensitivity reactions with IV iron products, minimise this risk where possible and to ensure that patients are appropriately informed.

Please note that prescribing and safety information differs between IV iron products and individual summaries of product characteristics (SmPC) should be consulted before and during use as appropriate.

Precautions for use in pregnancy

There are no adequate and well-controlled trials in pregnant women. Studies in animals have shown reproductive toxicity.

Iron-deficiency anaemia occurring in the first trimester of pregnancy can usually be treated with oral iron (intravenous iron should not be used). The benefits of using IV iron products should be carefully weighed against the risks later in pregnancy. Anaphylactic/anaphylactoid reactions occurring with IV iron products may have consequences for both the mother and the foetus (e.g. foetal anoxia, distress, death).

The test dose

Previously a test dose has been recommended for some IV iron products. However, no accurate data are available to clearly support a protective effect of a test dose. The test dose may lead to false reassurance as allergic reactions may occur even in patients that had a negative test dose. **Consequently test doses are no longer recommended and are replaced with the risk minimisation recommendations above.** Caution is warranted with every dose of IV iron product that is given, even if previous administrations have been well tolerated. IV iron products should be administered in accordance with the product specific posology and method of administration described in the product information for each individual product. In case of a hypersensitivity reaction, healthcare professionals are advised to immediately discontinue treatment and consider appropriate medical therapy.

For more details see relevant sections in the attached Israeli SPC for Ferrlecit, as approved on April 2014.

Call for reporting

Any suspected adverse events should be reported to the following address: Pv.Israel@sanofi.com

Company contact point

Please review carefully the revised enclosed product information and contact us if you have any additional questions.

Yours sincerely,

sanofi-aventis Israel ltd

1. NAME OF THE MEDICINAL PRODUCT

Ferrlecit

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

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

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:
Ferric chloride hexahydrate
Sodium carbonate, anhydrous
Sodium carbonate decahydrate
Sodium gluconate
Water for injections

Contains 45 mg benzyl alcohol per ampoule (5 ml) (see sections 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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ferrlecit is indicated in adults and children 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 level of iron deficiency, adults are given one ampoule daily of 5 ml by slow intravenous injection or by infusion after dilution with physiological saline solution.

Not more than one ampoule should be given, even in exceptional cases such as marked iron deficiency after repeated autologous donation.

I.V. injections must always be given very slowly with the patient supine.

For preference, the product can also be given as an intravenous infusion over 20 to 30 minutes, diluted with 100 to 250 ml of physiological saline solution.

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).

Pediatric population

Due to lack of clinical data on safety and efficacy, Ferrlecit solution for injection is not recommended 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[1)] [kg] 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 should 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,
- Iron overload (haemochromatosis, chronic haemolysis) or iron utilisation disorders (sideroblastic anaemia, lead anaemia, thalassaemia),
- Severe inflammatory diseases of the liver or kidneys,

Due to the content of benzyl alcohol, Ferrlecit must not be given to premature babies or neonates.

Because of its sucrose content, this medicinal product must not be used in patients suffering from hereditary fructose intolerance, glucose-galactose malabsorption or saccharase-isomaltase deficiency.

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.

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 contained in Ferrlecit may cause toxic and anaphylactic reactions in infants and children up to 3 years of age.

The administration of medications containing benzyl alcohol to newborns or premature neonates has been associated with a fatal “Gasping Syndrome” (symptoms include a striking onset of gasping syndrome, hypotension, bradycardia, and cardio-vascular collapse).

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

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 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.

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

There are no studies of the effects of Ferrlecit on the ability to drive or operate machines.

4.8 Undesirable effects

The assessment of undesirable effects is based on the following frequencies:

Very common	(≥ 10%)
Common	(≥ 1% - < 10%)
Uncommon	(≥ 0.1% - < 1%)
Rare	(≥ 0.01% - < 0.1%)
Very rare	(< 0.01%)
Not known	(frequency cannot be estimated on the basis of the available data)

Blood and lymphatic system disorders

Very rare: haemolysis, haemoglobulinuria (on overload of the transferrin system)

Vascular disorders

Rare: hypotensive events even progressing to circulatory collapse

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

Rare: anaphylactic reactions with oedema at various sites in the body, also in the region of the face, oral cavity and pharynx (e.g., glottal oedema)

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.

Cardiac disorders

Palpitations

Nervous system disorders

Paraesthesia, dizziness, taste disorders

Gastrointestinal disorders

Nausea, abdominal pains

Musculoskeletal and connective tissue disorders

Pain in the chest and back, muscle and joint pain, especially in patients with rheumatic disorders

Vascular disorders

Hypertension, facial reddening

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

Rarely, benzyl alcohol can cause hypersensitivity reactions.

4.9 Overdose

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

If serum iron levels exceed 3 mg/l and the iron binding capacity of transferrin is exceeded, i.v. infusion of 1 to 2 g deferoxamine (maximum 16 mg/kg/hour) is recommended. The infusion should be repeated on the next day if necessary and 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 Information for Healthcare Professionals/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 foetotoxic effects occurred.

6. PHARMACEUTICAL PARTICULARS

6.1 Excipients

Sucrose, benzyl alcohol, water for injections

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 Special precautions for storage

Store at a temperature not exceeding 25°C and protect from light.

The prepared infusion solution is stable for 24 hours at room temperature.

Marketing Authorization Holder: sanofi-aventis Israel Ltd, 10 Beni Gaon St., Netanya 4250499

Manufacturer: Aventis Pharma S.A, UK or SANOFI - AVENTIS S.P.A., ITALY