Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Diafer 50 mg/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One millilitre of solution contains 50 mg iron as ferric derisomaltose.

A 2 ml ampoule contains 100 mg iron as ferric derisomaltose.

Excipient with known effect
Each ml contains up to 5.4 mg sodium, see section 4.4.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Dark brown, non transparent solution with pH 5.0-7.0 and an approximate osmolarity of 400 mOsm/l.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Diafer is indicated in adults for the treatment of iron deficiency in patients with chronic kidney disease on dialysis, when oral iron preparations are ineffective or cannot be used.

The diagnosis of iron deficiency should be based on appropriate laboratory tests (e.g. serum ferritin, serum iron, transferrin saturation or hypochromic red cells).

4.2 Posology and method of administration

Posology

Diafer may be administered as an up to 200 mg dosage with a maximum weekly administration of 1000 mg.If higher doses than 200 mg of iron are needed, other iron medicinal products intended for intravenous use should be used.

The iron dose must be individualised based on the clinical response to treatment including evaluation of haemoglobin, ferritin and transferrin saturation, concomitant treatment with an erythropoiesis stimulating agent (ESA) and the dose of ESA treatment. Targets may vary from patient to patient and depending on local guidelines.

Maintenance therapy with iv iron treatment may be given as small doses administered at regular intervals to maintain iron status tests stable within specific limits with the intent of avoiding development of iron deficiency or decline of iron test parameters below specific levels.

Paediatric population:

Diafer is not recommended for use in children and adolescents < 18 years due to insufficient data on safety and efficacy in children.

Method of administration:

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

Diafer 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 Diafer injection (see section 4.4).

Diafer can be administered either as an intravenous bolus injection or during a haemodialysis session directly into the venous limb of the dialyser. It may be administered undiluted or diluted in up to 20 ml sterile 0.9% sodium chloride.

Diafer should not be administered concomitantly with oral iron preparations, since the absorption of oral iron might be decreased (see section 4.5).

4.3 Contraindications

- Non-iron deficiency anaemia (e.g. haemolytic anaemia)
- Iron overload or disturbances in utilisation of iron (e.g. haemochromatosis, haemosiderosis)
- Hypersensitivity to the active substance, to Diafer or any of its excipients listed in section 6.1
- Known serious hypersensitivity to other parenteral iron products
- Decompensated liver disease

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).

Diafer 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 Diafer 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.

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 (alanine aminotransferase and/or aspartate aminotransferase > 3 times upper limit of normal) where iron overload is a precipitating factor, in particular Porphyria Cutanea Tarda (PCT). Careful monitoring of iron status is recommended to avoid iron overload.

Parenteral iron should be used with caution in case of acute or chronic infection.

Diafer should not be used in patients with ongoing bacteraemia.

Hypotensive episodes may occur if intravenous injection is administered too rapidly.

Caution should be exercised to avoid paravenous leakage when administrating Diafer. Paravenous leakage of Diafer at the injection site may lead to irritation of the skin and potentially long lasting brown discolouration at the site of injection. In case of paravenous leakage, the administration of Diafer must be stopped immediately.

This medicinal product contains up to 5.4 mg sodium per ml, equivalent to 0.27 % 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

As with all parenteral iron preparations the absorption of oral iron is reduced when administered concomitantly.
Parenteral iron may cause falsely elevated values of serum bilirubin and falsely decreased values of serum calcium.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is only limited data from the use of ferric derisomaltose in pregnant women from one study with 100 exposed pregnant women. A careful risk/benefit evaluation is therefore required before use during pregnancy.

Iron deficiency anaemia occurring in the first trimester of pregnancy can in many cases be treated with oral iron. Treatment with Diafer 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.

Breastfeeding
A clinical study with ferric derisomaltose administered to lactating women showed transfer of iron to the breast milk with mean iron concentrations within normal range at all samples times. At therapeutic doses of ferric derisomaltose no negative effects on the breastfed newborns/infants are anticipated.

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

4.7 Effects on ability to drive and use machines

Diafer has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The table presents the adverse drug reactions (ADRs) reported during Diafer treatment in clinical trials and in-market experience.

Acute, severe hypersensitivity reactions may occur with parenteral iron preparations. They usually occur within the first few minutes of administration and are generally characterised by the sudden onset of respiratory difficulty and / or cardiovascular collapse; fatalities have been reported. Other less severe manifestations of immediate hypersensitivity such as urticaria, rashes, itching and nausea may also occur. In pregnancy, associated foetal bradycardia may occur with parenteral iron preparations.

Fishbane reaction characterised by flushing in the face, acute chest and/or back pain and tightness sometimes with dyspnea in association with IV iron treatment may occur (frequency uncommon). This may mimic the early symptoms of an anaphylactoid/anaphylactic reaction. The infusion should be stopped and the patient's vital signs should be assessed. These symptoms disappear shortly after the iron administration is stopped. They typically do not reoccur if the administration is restarted at a lower infusion rate.

Distant skin discolouration has also been reported post marketing following IV iron administration.

Adverse drug reactions observed during clinical trials and post-marketing experience

System Organ Class	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1000 to <1/100)**	**Rare (≥1/10000 to <1/1000)**	**Very rare (<1/10000)**	**Not known**
Blood and lymphatic system disorders				Haemolysis	
Immune system disorders		Hypersensitivity, including severe reactions		Anaphylactoid/ anaphylactic reactions	
Nervous system disorders		Blurred vision, hypoesthesia, dysphonia dysgeusia	Loss of consciousness, seizure,	Headache, paresthesia	

			dizziness, restlessness, tremor, fatigue, altered mental status		
Ear and labyrinth disorders				Transient deafness	
Cardiac disorders			Arrhythmia, tachycardia	Foetal bradycardia, palpitations	Kounis syndrome
Vascular disorders			Hypotension	Hypertension	
Respiratory, thoracic and mediastinal disorders		Dyspnoea, bronchospasm	Chest pain		
Gastrointestinal disorders		Nausea, emesis, abdominal pain, constipation, dyspepsia	Diarrhoea		
Skin and subcutaneous tissue disorders		Flushing, pruritus, rash, urticaria	Angioedema, sweating		Skin discolouration
Musculoskeletal and connective tissue disorders		Muscle spasm, back pain	Myalgia, arthralgia		
General disorders and administration site conditions	Injection site reactions**	Feeling hot, pyrexia, soreness, inflammation near the injection site, local phlebitic reaction	Malaise		Influenza like illness*

* Influenza like illness whose onset may vary from a few hours to several days
** Includes the following preferred terms, i.e. injection site erythema, -swelling, -burning, -pain, -bruising, -discolouration, -extravasation, -irritation, -reaction

Description of selected adverse reactions
Delayed reactions may also occur with parenteral iron preparations and can be severe. They are characterised by arthralgia, myalgia and sometimes fever. The onset varies from several hours up to four days after administration. Symptoms usually last two to four days and settle spontaneously or following the use of simple analgesics.

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 HPRA Pharmacovigilance,
Website: www.hpra.ie.

4.9 Overdose

The ferric derisomaltose in Diafer has a low toxicity. The preparation is well tolerated and has a minimal risk of accidental overdosing.

Large doses of parenteral iron (500 mg or more) have been reported to give a brown colour to serum from a blood sample drawn four hours after administration.
Excessive therapy with parenteral iron can lead to excess iron storage and possibly iatrogenic hemosiderosis or hemochromatosis.
Monitoring of iron parameters such as serum ferritin may assist in recognising iron accumulation. Supportive measures such as chelating agents can be used.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Iron parenteral preparation, ATC code: B03AC

Diafer solution for injection is a colloid with strongly bound iron in spheroidal iron-carbohydrate particles.

The Diafer formulation contains iron in a complex that enables a controlled and slow release of bioavailable iron to iron-binding proteins with little risk of free iron.

Each particle consists of a matrix of iron(III) atoms and derisomaltose with an average molecular weight of 1000 Da and a narrow molecular weight distribution that is almost devoid of mono- and disaccharides.
INN name: Ferric derisomaltose (also known as iron(III) isomaltoside 1000).

The chelation of iron(III) with carbohydrate confers to the particles a structure resembling ferritin that is suggested to protect against the toxicity of unbound inorganic iron(III).

The iron is available in a non-ionic water-soluble form in an aqueous solution with pH between 5.0 and 7.0.

Evidence of a therapeutic response can be seen within a few days of administration of ferric derisomaltose as an increase in the reticulocyte count. Due to the slow release of bioavailable iron serum ferritin peaks within days after an intravenous dose of ferric derisomaltose and slowly returns to baseline after weeks.

5.2 Pharmacokinetic properties

The Diafer formulation contains iron in a strongly bound complex that enables a controlled and slow release of bioavailable iron to iron-binding proteins with little risk of free iron toxicity.

After administration of a single dose of ferric derisomaltose of 100 to 1000 mg of iron in pharmacokinetic studies, the iron injected or infused was cleared from the plasma with a half-life that ranged from 1 to 4 days. Renal elimination of iron was negligible.

Following intravenous administration, ferric derisomaltose is rapidly taken up by the cells in the reticuloendothelial system (RES), particularly in the liver and spleen from where iron is slowly released.

Circulating iron is removed from the plasma by cells of the reticuloendothelial system which split the complex into its components of iron and derisomaltose. The iron is immediately bound to the available protein moieties to form hemosiderin or ferritin, the physiological storage forms of iron, or to a lesser extent, to the transport molecule transferrin. This iron, which is subject to physiological control, replenishes haemoglobin and depleted iron stores.

Iron is not easily eliminated from the body and accumulation can be toxic. Due to the size of the complex, ferric derisomaltose is not eliminated via the kidneys. Small quantities of iron are eliminated in urine and faeces.

Derisomaltose is either metabolised or excreted.

5.3 Preclinical safety data

Iron complexes have been reported to be teratogenic and embryocidal in non-anaemic pregnant animals at high single doses above 125 mg iron/kg body weight. The highest recommended dose in clinical use is 20 mg iron/kg body weight.

In a fertility study with ferric derisomaltose in rats no effects on female fertility or male reproductive performance and spermatogenic parameters were found at the dose levels tested.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections
Sodium chloride
Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6

6.3 Shelf life

30 months

Shelf life after first opening of the container (undiluted):

From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately.

If not used immediately, in-use storage times and conditions are the responsibility of user.

Shelf life after dilution with sterile 0.9% sodium chloride:

From a microbiological point of view the product should be used immediately.

6.4 Special precautions for storage

Do not freeze.

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

6.5 Nature and contents of container

Type 1 glass ampoule.
Pack sizes: 1 x 2 ml, 5 x 2 ml, 10 x 2 ml, 25 x 2 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Inspect ampoules visually for sediment and damage before use. Use only those containing sediment-free, homogeneous solution.

Diafer is for single use only and any unused solution or waste material should be disposed of in accordance with local requirements.

Diafer must only be mixed with sterile 0.9% sodium chloride. No other intravenous dilution solutions should be used. No other therapeutic agents should be added. For dilution instructions, see section 4.2.

The diluted solution for injection should be visually inspected prior to use. Use only clear solutions without sediment.

7 MARKETING AUTHORISATION HOLDER

Pharmacosmos A/S
Roervangsvej 30
DK-4300 Holbaek
Denmark

8 MARKETING AUTHORISATION NUMBER

PA0982/004/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 9th May 2014
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10 DATE OF REVISION OF THE TEXT

October 2025