Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT (FPP)

Amifer® IV

1.1. Strength

20mg iron/ml

1.2. Pharmaceutical form

Solution for injection or concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1. Qualitative declaration

Each 5ml ampoule of Amifer IV contains 100mg iron as iron sucrose (iron(III)-hydroxide sucrose complex).

For the full list of excipients, see section 6.1.

2.2. Quantitative declaration

One milliliter of solution contains 20mg of iron as iron sucrose.

3. PHARMACEUTICAL FORM

Solution for injection or concentrate for solution for infusion.

Amifer IV is a dark brown, non-transparent, aqueous solution

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Amifer IV is indicated for the treatment of iron deficiency in the following indications:

- Where there is a clinical need for a rapid iron supply,
- In patients who cannot tolerate oral iron therapy or who are non-compliant,
- In active inflammatory bowel disease where oral iron preparations are ineffective,
- In chronic kidney disease when oral iron preparations are less effective.

The diagnosis of iron deficiency must be based on appropriate laboratory tests (e.g. Hb, serum ferritin, TSAT, serum iron, etc.).

(*Hb= haemoglobin, TSAT =transferrin saturation)*

4.2. Posology and mode of administration

4.2.1. Posology

Amifer IV 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 Amifer IV administration (see section 4.4)
The cumulative dose of Amifer IV must be calculated for each patient individually and must not be exceeded.

Calculation of dosage:
The total cumulative dose of Amifer IV, equivalent to the total iron deficit (mg), is determined by the haemoglobin level (Hb) and body weight (BW). The dose of Amifer IV must be individually calculated for each patient according to the total iron deficit calculated with the following Ganzoni formula, for example:

Total iron deficit [mg] = BW [kg] x (target Hb – actual Hb) [g/dl] x 2.4* + storage iron [mg]

- Below 35 kg BW: Target Hb = 13 g/dl and storage iron = 15 mg/kg BW
- 35 kg BW and above: Target Hb = 15 g/dl and storage iron = 500mg

*Factor 2.4 = 0.0034 (iron content of Hb = 0.34%) x 0.07 (blood volume = 7% of BW) x 1000 (conversion of [g] to [mg]) x 10

Total Amifer IV to be administered (in ml) = Total iron deficit [mg] / 20mg iron/ml

Total amount of Amifer IV (ml) to be administered according to the body weight, actual Hb level and target Hb level*:

BW	**Total amount of Amifer IV (20 mg of iron per ml) to be administered**			
	Hb 6.0 g/dl	**Hb 7.5 g/dl**	**Hb 9.0 g/dl**	**Hb 10.5 g/dl**
30 kg	47.5 ml	42.5 ml	37.5 ml	32.5 ml
35 kg	62.5 ml	57.5 ml	50 ml	45 ml
40 kg	67.5 ml	60 ml	55 ml	47.5 ml
45 kg	75 ml	65 ml	57.5 ml	50 ml
50 kg	80 ml	70 ml	60 ml	52.5 ml
55 kg	85 ml	75 ml	65 ml	55 ml
60 kg	90 ml	80 ml	67.5 ml	57.5 ml
65 kg	95 ml	82.5 ml	72.5 ml	60 ml
70 kg	100 ml	87.5 ml	75 ml	62.5 ml
75 kg	105 ml	92.5 ml	80 ml	65 ml
80 kg	112.5 ml	97.5 ml	82.5 ml	67.5 ml
85 kg	117.5 ml	102.5 ml	85 ml	70 ml
90 kg	122.5 ml	107.5 ml	90 ml	72.5 ml

*Below 35 kg BW: Target Hb = 12 g/dl
35 kg BW and above: Target Hb = 15 g/dl
To convert Hb (mM) to Hb (g/dl), multiply the former by 1.6.

If the total necessary dose exceeds the maximum allowed single dose, then the administration must be divided.

Adults: 5 – 10ml of Amifer IV (100 – 200mg iron) 1 to 3 times a week. For administration time and dilution ratio see “Method of administration”.

4.2.2. Special populations

See sections 4.2.1 and 4.4.1

4.2.3. Pediatric population

The use of Amifer IV has not been adequately studied in children and, therefore, Amifer IV is not recommended for use in children.

4.2.4. Method of administration

Amifer IV must only be administered by the intravenous route. This may be by a slow intravenous injection, by an intravenous drip infusion or directly into the venous line of the dialysis machine.

Intravenous drip infusion:

Amifer IV must only be diluted in sterile 0.9% m/V sodium chloride (NaCl) solution. Dilution must take place immediately prior to infusion and the solution should be administered as follows:

Amifer IV dose (mg of iron)	**Amifer IV dose (ml of Amifer IV)**	**Maximum dilution volume of sterile 0.9% m/V NaCl solution**	**Minimum Infusion Time**
50 mg	2.5 ml	50 ml	8 minutes
100 mg	5 ml	100 ml	15 minutes
200 mg	10 ml	200 ml	30 minutes

For stability reasons, dilutions to lower Amifer IV concentrations are not permissible.

Intravenous injection:

Amifer IV may be administered by slow intravenous injection at a rate of 1 ml undiluted solution per minute and not exceeding 10 ml Amifer IV (200 mg iron) per injection.

Injection into venous line of dialysis machine:

Amifer IV may be administered during a haemodialysis session directly into the venous line of the dialysis machine under the same conditions as for intravenous injection.

4.3. Contraindications

The use of Amifer IV is contraindicated in the following conditions:

- Hypersensitivity to the active substance, to Amifer IV or any of its excipients listed in section 6.1
- Known serious hypersensitivity to other parenteral iron products
- Anaemia not caused by iron deficiency
- Evidence of iron overload or hereditary disturbances in utilisation of iron.

4.4. Special warning and precautions for use

4.4.1. General information

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 iron sucrose. However, in several studies performed in patients who had a history of a hypersensitivity reaction to iron dextran or ferric gluconate, Amifer IV was shown to be well tolerated. For known serious hypersensitivity to other parenteral iron product see section 4.3.

The risk of hypersensitivity reactions 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).

Amifer IV 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 Amifer IV 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 risk/benefit 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.

Parenteral iron should be used with caution in the case of acute or chronic infection. It is recommended that the administration of Amifer IV is stopped in patients with bacteraemia. In patients with chronic infection, a risk/benefit evaluation should be performed.

Paravenous leakage must be avoided because leakage of Amifer IV at the injection site can lead to pain, inflammation and brown discoloration of the skin.

4.4.2. Pediatric population

The use of Amifer IV has not been adequately studied in children and, therefore, Amifer IV is not recommended for use in children.

4.5. Interactions with other medicinal products and other forms of interactions

4.5.1. General information

As with all parenteral iron preparations, Amifer IV should not be administered concomitantly with oral iron preparations since the absorption of oral iron is reduced. Therefore, oral iron therapy should be started at least 5 days after the last injection of Amifer IV.

4.5.2. Additional information on special populations

No specific information available

4.5.3. Pediatric population

No specific information available

4.6. Fertility, pregnancy and lactation

4.6.1. Pregnancy

There is no data from the use of iron sucrose in pregnant women in the first trimester. Data (303 pregnancy outcomes) from the use of iron-sucrose in pregnant women in the second and third trimester showed no safety concerns for the mother or newborn.

A careful risk/benefit evaluation is required before use during pregnancy and Amifer IV 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 Amifer IV 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 do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

4.6.2. Lactation

There is limited information on the excretion of iron in human milk following administration of intravenous iron sucrose. In one clinical study, 10 healthy breast-feeding mothers with iron deficiency received 100 mg iron in the form of iron sucrose. Four days after treatment, the iron content of the breast milk had not increased and there was no difference from the control group (n=5). It cannot be excluded that newborns/infants may be exposed to iron derived from Amifer IV via the mother's milk, therefore the risk/benefit should be assessed.

Preclinical data do not indicate direct or indirect harmful effects to the nursing child. In lactating rats treated with ^{59}Fe labelled iron sucrose, low secretion of iron into the milk and transfer of iron into the offspring was observed. Non metabolised iron sucrose is unlikely to pass into the mother's milk.

4.6.3. Fertility

No effects of iron sucrose treatment were observed on fertility and mating performance in rats.

4.7. Effects on the ability to drive and use machines

In the case of symptoms of dizziness, confusion or light headedness following the administration of Amifer IV, patients should not drive or use machinery until the symptoms have ceased.

4.8. Undesirable effects

The most commonly reported adverse drug reaction in clinical trials with intravenous iron sucrose was dysgeusia, which occurred with a rate of 4.5 events per 100 subjects. The most important serious adverse drug reactions associated with intravenous iron sucrose are hypersensitivity reactions, which occurred with a rate of 5% subjects in clinical trials.

Anaphylactoid reactions are uncommon and consist of hives, rashes, pruritus, nausea and chills. When signs of anaphylactoid reactions are observed, administration should be stopped immediately. Severe acute anaphylactoid reactions are very rare. They usually occur within the first few minutes of administration and are usually characterised by sudden onset of respiratory difficulty and / or cardiovascular collapse; deaths have been reported.

Delayed reactions have been described and can be severe. They are characterised by arthralgia, myalgia and sometimes fever. They occur between a few hours and up to four days after administration. The symptoms usually last 2 to 4 days and disappear spontaneously or under the effect of peripheral analgesics.

In rheumatoid arthritis, joint pain may increase. Local reactions such as pain and inflammation at the injection site or in proximity of the injection site as well as local phlebitis reactions have been reported.

The adverse drug reactions reported after the intravenous administration of iron-sucrose solution in 4,064 subjects in clinical trials as well as those reported from the post-marketing setting are presented in the table below.

System organ class	**Common (≥1/100, <1/10)**	**Uncommon (≥1/1000, <1/100)**	**Rare (≥1/10000, <1/1000)**	**Frequency not known (**cannot be estimated on the basis of the available data)
Immune system disorders		Hypersensitivity		Anaphylactoid reactions, angioedema
Nervous system disorders	Dysgeusia	Headache, dizziness, paraesthesia, hypoaesthesia	Syncope, somnolence	Depressed level of consciousness, confusional state, loss of

System organ class	Common (≥1/100, <1/10)	Uncommon (≥1/1000, <1/100)	Rare (≥1/10000, <1/1000)	Frequency not known (cannot be estimated on the basis of the available data)
				consciousness, anxiety, tremor
Cardiac disorders			Palpitations	Bradycardia, tachycardia
Vascular disorders	Hypotension, hypertension	Flushing, phlebitis		Circulatory collapse, thrombophlebitis
Respiratory, thoracic and mediastinal disorders		Dyspnoea		Bronchospasm
Renal and urinary disorders			Chromaturia	
Gastrointestinal disorders	Nausea	Vomiting, abdominal pain, diarrhea, constipation		
Skin and subcutaneous tissue disorders		Pruritus, rash		Urticaria, erythema
Musculoskeletal and connective tissue disorders		Muscle spasm, myalgia, arthralgia, pain in extremity, back pain		
General disorders and administration site conditions	Injection/infusion site reaction [1)]	Chills, asthenia, fatigue, oedema peripheral, pain	Chest pain, hyperdrosis, pyrexia	Cold sweat, malaise, pallor
Investigations		Alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, serum ferritin increased	Blood lactate dehydrogenase increased	

[1)] The most frequently reported are: injection/infusion site pain, -extravasation, -irritation, -reaction, -discolouration, -haematoma, -pruritus.

4.9. Overdose

Overdose can cause iron overload which may manifest itself as haemosiderosis. Overdose should be treated, as deemed necessary by the treating physician, with an iron chelating agent or according to standard medical practice.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group and ATC code :

Pharmacotherapeutic group: Anti-anaemic preparation, iron, parenteral preparation

ATC code: B03AC

Mechanism of action

The polynuclear iron core has a structure similar to that of the core of the physiological iron storage protein ferritin. The complex is designed to provide, in a controlled manner, utilisable iron for the iron transport and storage proteins in the body (i.e., transferrin and ferritin, respectively). Following intravenous administration, the polynuclear iron core from the complex is taken up predominantly by the reticuloendothelial system in the liver, spleen, and bone marrow. In a second step, the iron is used for the synthesis of Hb, myoglobin and other iron-containing enzymes, or stored primarily in the liver in the form of ferritin.

Clinical efficacy and safety

Chronic kidney disease

A single arm study was to investigate the efficacy and safety of 100 mg iron as iron sucrose for up to 10 sessions over 3-4 weeks in haemodialysis patients with iron deficiency anaemia (Hb >8 and <11.0 g/dl, TSAT <20%, and serum ferritin ≤300 µg/l) who were receiving rHuEPO therapy. A Hb ≥11 g/dl was attained in 60/77 patients. The mean increase in serum ferritin and TSAT was significant from baseline to the end of treatment (Day 24) as well as to the 2 and 5 weeks follow-up visit.

A randomised study was comparing iron sucrose (1000 mg in divided doses over 14 days) and oral ferrous sulphate (325 mg 3 times daily for 56 days) in non-dialysis dependent chronic kidney disease patients (Hb ≤11.0 g/dl, serum ferritin ≤300 µg/l, and TSAT ≤25%) with or without rHuEPO. A clinical response (defined as Hb increase ≥1.0 g/dl and serum ferritin increase ≥160 µg/l) was more frequently observed in patients treated with iron sucrose (31/79; 39.2%) compared to oral iron (1/82; 1.2%); p<0.0001.

Inflammatory Bowel Disease

A randomised, controlled study compared iron sucrose (single IV dose of 200 mg iron once per week or every second week until the cumulative dose was reached) with oral iron (200 mg twice daily for 20 weeks) in patients with inflammatory bowel disease and anaemia (Hb <11.5 g/dl). At the end of treatment, 66% of patients in the iron sucrose group had an increase in Hb ≥2.0 g/dl compared to 47% in the oral iron group (p=0.07).

Postpartum

A randomised, controlled trial in women with postpartum iron deficiency anaemia (Hb <9 g/dl and serum ferritin <15 µg/l at 24–48 hours post-delivery) compared 2 × 200 mg iron given as iron sucrose on Days 2 and 4 (n=22) and 200 mg of oral iron given as ferrous sulphate twice daily for 6 weeks (n=21). The mean increase in Hb from baseline to Day 5 was 2.5 g/dl in the iron sucrose group and 0.7 g/dl in the oral iron group (p<0.01).

Pregnancy

In a randomised, controlled study, women in their third trimester of pregnancy with iron deficiency anaemia (Hb 8 to 10.5 g/dl and serum ferritin <13 µg/l) were randomised to iron sucrose (individually calculated total dose of iron administered over 5 days) or oral iron polymaltose complex (100 mg 3× daily until delivery). The increase in Hb from baseline was significantly greater in the iron sucrose group compared to the oral iron group at Day 28 and at delivery (p<0.01).

5.2. Pharmacokinetic properties

Distribution

The ferrokinetics of iron sucrose labelled with ^{52}Fe and ^{59}Fe were assessed in 6 patients with anaemia and chronic renal failure. In the first 6–8 hours, ^{52}Fe was taken up by the liver, spleen and bone marrow. The radioactive uptake by the macrophage-rich spleen is considered to be representative of the reticuloendothelial iron uptake.

Following intravenous injection of a single 100 mg iron dose of iron sucrose in healthy volunteers, maximum total serum iron concentrations were attained 10 minutes after injection and had an average concentration of 538 µmol/l. The volume of distribution of the central compartment corresponded well to the volume of plasma (approximately 3 litres).

Biotransformation

Upon injection, sucrose largely dissociates and the polynuclear iron core is mainly taken up by the reticuloendothelial system of the liver, spleen, and bone marrow. At 4 weeks after administration, red cell iron utilization ranged from 59 to 97%.

Elimination

The iron sucrose complex has a weight average molecular weight (Mw) of approximately 43 kDa, which is sufficiently large to prevent renal elimination. Renal elimination of iron, occurring in the first 4 hours after injection of a Amifer IV dose of 100 mg iron, corresponded to less than 5% of the dose. After 24 hours, the total serum iron concentration was reduced to the pre-dose level. Renal elimination of sucrose was about 75% of the administered dose.

5.3. Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity and toxicity to reproduction and development.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Water for injections

Sodium hydroxide (for pH adjustment)

6.2. Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6. There is the potential for precipitation and/or interaction if mixed with other solutions or medicinal products. The compatibility with containers other than glass, polyethylene and PVC is not known.

6.3. Shelf life

Shelf life of Amifer IV as packaged for sale

24 months

Shelf life after first opening of the container

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

Shelf life after dilution with sterile 0.9% m/V sodium chloride (NaCl) solution

From a microbiological point of view, the product should be used immediately after dilution with sterile 0.9% m/V sodium chloride solution.

6.4. Special precautions for storage

Store below 30°C. Do not freeze. Store in the original package.

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

6.5. Nature and contents of container

5 ml solution in one colorless glass ampoule (type I glass) in pack size of 5 ampoules.

6.6. Special precautions for disposal and other handlings

The ampoules should be visually inspected for sediment and damage before use. Use only those containing a sediment free and homogenous solution.

Amifer IV must not be mixed with other medicinal products except sterile 0.9% m/V sodium chloride solution for dilution.

For instructions on dilution of the product before administration, see section 4.2.

The diluted solution must appear as brown and clear.

Each ampoule or vial of Amifer IV is intended for single use only.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Any unused solution residue must be discarded.

7. MARKETING AUTHORISATION HOLDER AND MANUFACURING SITE ADDRESS

7.1. Marketing Authorisation Holder

Dafra Pharma GmbH, Mühlenberg 7, 4052 Basel, Switzerland

7.2. Manufacturer

Manufacturing site: Mefar Ilaç Sanayii A.Ş. Ramazanoğlu Mah. Ensar Cad. N°20 ; Kurtköy-Pendik, Istanbul, Turkey

Released by: Santa Farma İlaç Sanayi A.Ş.

8. MARKETING AUHORISATION NUMBER

8.1. Burundi : Klik hier als u tekst wilt invoeren.

8.2. Kenya: Klik hier als u tekst wilt invoeren.

8.3. Rwanda: Klik hier als u tekst wilt invoeren.

8.4. Tanzania: Klik hier als u tekst wilt invoeren.

8.5. Uganda: Klik hier als u tekst wilt invoeren.

9. DATE OF FIRST REGISTRATION

9.1. Burundi: Klik hier als u tekst wilt invoeren.

9.2. Kenya: Klik hier als u tekst wilt invoeren.

9.3. Rwanda: Klik hier als u tekst wilt invoeren.

9.4. Tanzania: Klik hier als u tekst wilt invoeren.

9.5. Uganda: Klik hier als u tekst wilt invoeren.

10. DATE OF REVISION OF TEXT

January 2018

11. DOSIMETRY (if applicable)

Not applicable

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (if applicable)

Not applicable