PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

CosmoFer 50 mg solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains iron (III)–hydroxide dextran complex

equivalent to 50 mg iron (III).

Contains no preservatives.

Contains sugar: Approximately 20 % *w/v* low molecular weight dextran.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection/infusion

CosmoFer is a dark brown solution filled into a 2 ml or 10 ml clear glass ampoule.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Severe iron deficiency in adult patients, intolerant to or not responding to oral iron when confirmed by appropriate investigations.

4.2 Posology and method of administration

Posology

Anaphylactoid reactions to **CosmoFer** are usually evident within a few minutes, and close observation is necessary to ensure recognition.

Patients should be carefully monitored for signs and symptoms of hypersensitivity reactions during and following each administration of **CosmoFer.**

CosmoFer should only be administered when staff trained to evaluate and manage anaphylactic reactions is immediately available, in an environment where full resuscitation facilities is assured.

The patient should be observed for adverse effects for at least 60 minutes following each **CosmoFer** injection. (see section 4.4).

If at any time during the intravenous administration of **CosmoFer**, any signs of a hypersensitivity reaction or intolerance are detected, administration must be stopped immediately.

Special Populations

Children (under 14 years): CosmoFer should not be used for children. There is no documentation for efficacy and safety.

Elderly patients: No specific dose adjustment for the use of **CosmoFer** in older people (≥ 65 years) is recommended (see “Method of administration”).

Patients with renal impairment: No specific dose adjustment is required, except in cases of acute renal failure where the use of **CosmoFer** is contraindicated (refer to section 4.3).

Patients with hepatic impairment: No specific dose adjustment is required, except for patients with decompensated liver cirrhosis and hepatitis where the use of **CosmoFer** is contraindicated (refer to section 4.3).

Method of administration:

CosmoFer solution for injection/infusion can be administered by an intravenous drip infusion or by a slow intravenous injection of which the intravenous drip infusion is the preferred route of administration, as this may help to reduce the risk of hypotensive episodes. However, **CosmoFer** may also be administered as undiluted solution intramuscularly.

Adults and elderly:

The total cumulative dose of **CosmoFer** is determined by haemoglobin level and body weight. The dose and dosage schedule for **CosmoFer** must be individually estimated for each patient based on a calculation of the total iron deficit.

Dosage: The normal recommended dosage schedule is 100 to 200 mg of iron corresponding to 2 to 4 ml, two or three times a week depending on the haemoglobin level. The **CosmoFer** injection should not be administered concomitantly with oral iron preparations as the absorption of oral iron will be reduced (see section 4.5).

Intravenous Drip Infusion:

CosmoFer must be diluted only in 0,9 % sodium chloride solution (normal saline) or in 5 % glucose solution. **CosmoFer** in a dose of 100 to 200 mg elemental iron (2 to 4 ml) may be diluted in 100 ml. On each occasion, the first 25 mg of iron should be infused over a period of 15 minutes. If no adverse reactions occur during this time, the remaining portion of the infusion should be given at an infusion rate of not more than 100 ml in 30 minutes.

Intravenous Injection:

CosmoFer may be administered in a dose of 100 to 200 mg iron (2 to 4 ml) by slow intravenous injection (0,2 ml/min) preferably diluted in 10 to 20 ml of 0,9 % sodium chloride or 5 % glucose solution. On each occasion, before administering a slow intravenous

injection, 25 mg of **CosmoFer** (0,5 ml) should be injected slowly over a period of 1 to 2 minutes. If no adverse reactions occur within 15 minutes, the remaining portion of the injection may be given.

Total Dose Infusion:

Immediately before administration, the total **CosmoFer** required, determined from the dosage table or by calculation, is added aseptically to the required volume, usually 500 ml of sterile 0,9 % sodium chloride or 5 % glucose solutions. The total amount of **CosmoFer,** up to 20 mg/kg body weight, is infused intravenously over 4 to 6 hours. The first 25 mg of iron should be infused over a period of 15 minutes. The patient must be kept under close medical observation during this period. If no adverse reactions occur during this time, then the remaining portion of the infusion should be given. The rate of infusion may be increased progressively to 45 to 60 drops per minute (based on a standard infusion set delivering 20 drops/ml of 0,9 % sodium chloride or 5 % glucose).

Patients should be observed carefully during the infusion and for at least 1 hour after completion. Total Dose Infusion (TDI) has been associated with an increased incidence of adverse reactions, in particular delayed hypersensitivity - like reactions.

The intravenous administration of CosmoFer by the Total Dose Infusion method should be restricted to hospital use only.

Injection into Dialyser:

CosmoFer may be administered during a haemodialysis session directly into the venous limb of the dialyser under the same procedures as outlined for intravenous administration.

Intramuscular Injection:

The total amount of **CosmoFer** required is determined either from the dosage table or by calculation. It is administered as a series of undiluted injections of up to 100 mg iron (2,0 ml) each determined by the patient's body weight. If the patient is moderately active, injections may be given daily into alternate buttocks. In inactive or bedridden patients, the frequency of injections should be reduced to once or twice a week.

CosmoFer must be given by deep intramuscular injection to minimise the risk of subcutaneous staining. It should be injected only into the muscle mass of the upper outer quadrant of the buttocks, never into the arm or other exposed areas.

The patient should be lying in the lateral position with the injection site uppermost or standing bearing their weight on the leg opposite the injection site. To avoid injection or leakage into the subcutaneous tissue, a Z-track technique is recommended. **CosmoFer** is injected slowly. It is important to wait for a few seconds before withdrawing the needle to allow the muscle mass to accommodate the injection volume. To minimise leakage up the injection track, the patient should be encouraged not to rub the injection site.

Calculation of Dose

a) Iron replacement in patients with iron deficiency anaemia

Factors contributing to the formula are shown below. The required dose has to be individually adapted according to the total iron deficit calculated by the following formula (haemoglobin in g/l or mmol/l).

Total dose (mg Fe) – Hb in g/l:

(Body weight (kg) x (target Hb – actual Hb) (g/l) x 0,24) + mg iron for iron stores

The factor 0,24 is derived from the following assumptions:

a) Blood volume 70 ml/kg of body weight ≈ 7 % of body weight

b) Iron content of haemoglobin 0,34 %

Factor 0,24 = 0,0034 x 0,07 x 1000 (conversion from g to mg).

Total dose (mg Fe) – Hb in mmol/l:

(Body weight (kg) x (target Hb in mmol/l – actual Hb in mmol/l) x 3,84) + mg iron for iron stores.

The factor 3,84 is derived from the following assumptions:

a) Blood volume 70 ml/kg of body weight ≈ 7 % of body weight

b) Iron content of haemoglobin 0,34 %

c) Factor for conversion from haemoglobin g/l to mmol/l is 0,06205

Factor 3,84 = 0,0034 x 0,07 x 1 000 / 0,06205

The table below shows the number of millilitres of **CosmoFer** solution for injection/infusion to be used at various degrees of iron deficiency anaemia.

The figures in the table below are based on a target haemoglobin of 150 g/l or 9,3 mmol/l and iron stores of 500 mg which apply to a body weight exceeding 35 kg.

Although there are significant variations in body build and weight distribution among males and females, the accompanying table and formula represent a convenient means for estimating the total iron required. This total iron requirement reflects the amount of iron needed to restore haemoglobin concentration to normal or near normal levels plus an additional allowance to provide adequate replenishment of iron stores in most individuals with moderately or severely reduced levels of haemoglobin. It should be remembered that iron deficiency anaemia will not appear until essentially all iron stores have been depleted.

Therapy, thus, should aim at not only replenishment of haemoglobin iron but of iron stores as well. If the total necessary dose exceeds the maximum allowed daily dose, the

administration has to be split. Evidence of a therapeutic response can be seen within a few days of administration of **CosmoFer** as an increase in the reticulocyte count.

Serum ferritin levels usually provide a good guide to the replenishment of iron stores. In renal dialysis patients receiving **CosmoFer**, this correlation may not be valid.

Total dose of CosmoFer in Millilitres to be administered in iron deficiency anaemia

Haemoglobin content	**60 g/l ≈ 3,7 mmo/l**	**75 g/l ≈ 4,7 mmol/l**	**90 g/l ≈ 5,6 mmol/l**	**105 g/l ≈ 6,5 mmol/l**	**120 g/l ≈ 7,4 mmol/l**	**135 g/l ≈ 8 mmol/l**
Bodyweight (kg)						
35	25	23	20	18	15	12,5
40	27	24	22	19	16	13
45	29	26	23	20	16,5	13
50	32	28	24	21	17	13,5
55	34	30	26	22	18	14
60	36	32	27	23	18,5	14,5
65	38	33	29	24	19,5	14,5
70	40	35	30	25	20	15
75	42	37	32	26	21	15,5
80	45	39	33	27	21,5	16
85	47	41	34	28	22	16
90	49	42	36	29	23	16,5

Note: The table and accompanying formula are applicable for dose determination only in patients with iron deficiency anaemia. They are not to be used for dose determination in patients requiring iron replacement for blood loss.

b) Iron replacement for blood loss

Iron therapy in patients with blood loss should be directed towards replacement of an amount of Iron equivalent to the amount of iron represented in the blood loss.

The table and formula described are not applicable for simple iron replacement values. Quantitative estimates of the individual's periodic blood loss and haematocrit during the bleeding episode provide a convenient method of calculation of the required iron dose.
The required **CosmoFer** dose to compensate the iron deficit is calculated according to the following formulas:

- If the volume of blood lost is unknown: The administration of 200 mg I.V. iron (4 ml **CosmoFer**) results in an increase of haemoglobin which is equivalent to 1 unit blood (= 400 ml with 150 g/l Hb content or 9,3 mmol Hb/l – equivalent to 0,34 % of 0,4 x 150 or 204 mg iron).

  Iron to be replaced mg = number of blood units lost x 200.

  Millilitres of **CosmoFer** needed = number of blood units lost x 4.
- If the Hb level is reduced: Use the previous formula considering that the depot iron does not need to be restored.

mg iron to be replaced = body weight (kg) x 0,24 x (target Hb in g/l – actual Hb in g/l).

OR

mg iron to be replaced = body weight (kg) x 3,84 x (target Hb in mmol/l – actual Hb in mmol/l).

e.g.: body weight 60 kg, Hb deficit = 10 g/l or 0,62 mmol/l:

Iron to be replaced = 60 x 0,24 x 10 = 60 x 3,84 x 0,62 = 143 mg (≈ 3 millilitres **CosmoFer**)

4.3 Contraindications

- Hypersensitivity to the active substance, to **CosmoFer** or any of the excipients (see

section 6.1).

- Known hypersensitivity to other parenteral iron products.
- Non-iron deficiency anaemia e.g., haemolytic anaemia and anaemia of chronic disease.
- Iron overload or disturbances in utilisation of iron (e.g. haemochromatosis, haemosiderosis).
- Patients with a history of allergies such as of asthma, eczema, or other atopic allergy
- Decompensated liver cirrhosis and hepatitis.
- Acute or chronic infection because parenteral iron administration may exacerbate bacterial or viral infections.
- Rheumatoid arthritis with symptoms or signs of active inflammation.
- Acute renal failure.

4.4 Special warnings and precautions for use

Parenterally administered iron preparations, such as **CosmoFer** can cause hypersensitivity reactions including serious and potentially fatal anaphylactic/anaphylactoid reactions.

Hypersensitivity reactions have also been reported after previously uneventful doses of **CosmoFer.**

The risk is enhanced for patients with known allergies including medicine 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).

CosmoFer 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 60 minutes following each **CosmoFer** 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 1:1 000 epinepherine (adrenaline) solution. Additional treatment with antihistamines and/or corticosteroids should be given as appropriate.

The intramuscular and subcutaneous injection of iron-carbohydrate complexes in very large doses under experimental conditions in animals produced sarcoma in rats, mice, rabbits, possibly hamsters but not in guinea pigs. Cumulative information and independent assessment indicate that the risk of sarcoma formation in man is minimal.

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

4.5 Interaction with other medicines and other forms of interaction

The **CosmoFer** injection should not be administered concomitantly with oral iron preparations as the absorption of oral iron will be reduced. Oral iron therapy should not be started earlier than 5 days after the last injection of **CosmoFer**.

Large doses of **CosmoFer** (5 ml or more) have been reported to give a brown colour to serum from a blood sample drawn four hours after administration.

CosmoFer may cause falsely elevated values of serum bilirubin and falsely decreased values of serum calcium.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well controlled trials on safety from the use of **CosmoFer** in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

A careful risk/benefit evaluation is therefore required before use during pregnancy.

(See section 4.4).

Iron deficiency anaemia occurring in the first trimester of pregnancy can in most cases be treated with oral iron. Treatment with CosmoFer should be confined to second and third trimester.

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

Breastfeeding

It is unknown whether the complex iron-dextran is excreted in human or animal breast milk. It is preferable to not use **CosmoFer** during breastfeeding.

4.7 Effects on ability to drive and use machines

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

Adverse reactions such as blurred vision, dizziness, tremor may influence ability to drive and use machines.

4.8 Undesirable effects

a. Summary of the safety profile

Approximately 5 % of patients can be expected to experience adverse reactions.

These are mainly dose dependent. Anaphylactoid reactions are uncommon and include urticaria, rashes, itching, nausea and shivering. Administration must be stopped immediately when signs of an anaphylactoid reaction are observed.

Acute, severe anaphylactoid reactions may occur. 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. However, patients should be observed for at least 60 minutes after administration of **CosmoFer.**

Delayed reactions are well described and may 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.

Exacerbation of joint pain in rheumatoid arthritis can occur. Local reactions reported are soreness and inflammation at or near injection site and local phlebitic reaction. Local complications at the injection site after intramuscular injection such as staining of the skin, bleeding, formation of sterile abscesses, tissue necrosis or atrophy and pain may occur.

b. Tabulated summary of adverse reactions

MedDRA system organ class	**Uncommon** (> 1/1 000; < 1/100)	**Rare** (> 1/10 000; < 1/1000)	**Very rare** (< 1/10 000)	**Not Known**
Blood and lymphatic system disorders			Haemolysis	
Cardiac Disorders		Dysrhythmia Tachycardia	Foetal bradycardia, palpitations	
Ear and labyrinth disorders			Transient deafness	

MedDRA system organ class	**Uncommon** (> 1/1 000; < 1/100)	**Rare** (> 1/10 000; < 1/1000)	**Very rare** (< 1/10 000)	**Not Known**
Gastrointestinal disorders	Nausea, vomiting, abdominal pain	Diarrhoea		
General disorders and administration site conditions	Feeling hot	Fatigue Pain and brown pigmentation at injection site		Influenza like illness whose onset may vary from a few hours to several days
Immune system disorders	Anaphylactoid / anaphylactic reactions including dyspnoea, urticaria, rashes, itching, nausea, shivering and	Angioedema,		

MedDRA system organ class	**Uncommon** (> 1/1 000; < 1/100)	**Rare** (> 1/10 000; < 1/1000)	**Very rare** (< 1/10 000)	**Not Known**
	cardiovascular collapse			
Musculoskeletal and connective tissues disorders	Cramps	Myalgias		
Nervous system disorders	Blurred vision, numbness	Loss of consciousness, seizures, dizziness, restlessness, tremor	Headache, paraesthesia	
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Chest pain		
Psychiatric disorders		Mental status changes		
Skin and subcutaneous tissue disorders	Flushing, pruritus, rash	Sweating		
Vascular		Hypotension	Hypertension	

MedDRA system organ class	**Uncommon** (> 1/1 000; < 1/100)	**Rare** (> 1/10 000; < 1/1000)	**Very rare** (< 1/10 000)	**Not Known**
disorders				

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to Acino Pharma via email on drugsafety_za@acino.swiss OR SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

See section 4.8.

Iron (III)-hydroxide dextran complex, as in **CosmoFer** injection, has a very low toxicity. The preparation is well tolerated and has a minimal risk of accidental overdosing.

Overdose can cause acute iron overloading which may manifest itself as haemosiderosis. Particular caution should be exercised to avoid iron overload where anaemia, unresponsive to treatment, has been incorrectly diagnosed as iron deficiency anaemia.

Supportive measures such as an iron chelating agent can be used.

With chronic repeated administration of iron at high dose, the excess iron will accumulate in the liver and induce an inflammatory process, which may lead to fibrosis.

Further treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A.8.3 Erythropoietics (Haematinics)

Pharmacotherapeutic group: Iron parenteral preparation, ATC code: B03AC.

The solution for injection/infusion contains iron as a stable iron(III)-hydroxide dextran complex, which is analogous to the physiological form of iron, ferritin (ferric hydroxide phosphate protein complex).

The iron is available in a non-ionic water-soluble form. It has a very low toxicity and can be given in large doses.

Serum ferritin peaks approximately 7 to 9 days after an intravenous dose of iron(III)–hydroxide dextran complex and slowly returns baseline after about 3 weeks.

Examination of the bone marrow for iron stores may not be meaningful for prolonged periods following iron dextran therapy because residual iron dextran may remain in the reticuloendothelial cells.

5.2 Pharmacokinetic properties

Following the IV infusion: The iron dextran is rapidly taken up by the cells in the reticuloendothelial system (RES), particularly in the liver and spleen from where iron is slowly released and bound to proteins. After administration an increased haematopoiesis can be observed for the next 6 to 8 weeks. The plasma half-life is 5 hours for circulating iron and 20 hours for total iron (bound and circulating).

Circulating iron is removed from the plasma by cells of the reticuloendothelial system which split the complex into its components of iron and dextran. The iron is immediately bound to the available protein moieties to form haemosiderin or ferritin, the physiological forms of iron, or to a lesser extent, to 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 (165,000 daltons) it is not eliminated via the kidneys. Small quantities of iron are eliminated in urine and faeces.
After intramuscular injection: Iron dextran is absorbed from the injection site into the capillaries and the lymphatic system. The major portion of the intramuscularly administered iron dextran is absorbed within 72 hours; most of the remaining iron is absorbed during the ensuing 3 to 4 weeks. Dextran is either metabolised or excreted.

5.3 Preclinical safety data

CosmoFer has been reported to be teratogenic and embryocidal in non-anaemic pregnant animals at high single doses above 125 mg/kg. The highest recommended dose in clinical use is 20 mg/kg. However, no detailed information is available from these studies.

In vitro and *in vivo* genotoxicity studies have showed mutagenic activity after the administration of high doses of iron-dextran complexes. However, the significance of these results is not clear. Iron dextran was not mutagenic at sub-toxic dose levels.

There are no other additional preclinical data of relevance to the prescriber than those already included in other sections of the Professional Information Leaflet.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid (for pH adjustment),

Sodium hydroxide (for pH adjustment),

Water for injection

6.2 Incompatibilities

CosmoFer must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

2 ml and 10 ml: 24 months

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

After dilution:

Chemical and physical in-use stability has been demonstrated for 24 hours at 25 °C after dilution with 0,9 % sodium chloride or 5 % glucose solution. From a microbiological point of view, the product should be used immediately.

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a cool dark place at or below 25 ºC. Store in the carton until required for use.

Do not freeze.

For storage of the diluted product, please refer to section 6.3.

6.5 Nature and contents of container

CosmoFer is packed into Type I clear 2 ml or 10 ml glass ampoules with break point. An outer carton box contains 2, 5 or 10 ampoules.

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, homogenous solution.

CosmoFer is for single use only and any unused solution should be discarded.

CosmoFer must not be mixed with other medicines for simultaneous administration. A 0,9 % sodium chloride solution or 5 % glucose solution are the only recommended diluents for an infusion.

7 HOLDER OF CERTIFICATE OF REGISTRATION

ACINO PHARMA (PTY) LTD

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8 REGISTRATION NUMBER

37/8/3/0434

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first approval: 15 August 2008

10 DATE OF REVISION OF THE TEXT

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