Applicant: Teva Pharmaceuticals (Pty) Ltd	**Product name: TEVIFER 100, TEVIFER 500 & TEVIFER 1000** **Dosage form & strength:** Solution for injection Each ml contains 50 mg of iron as ferric carboxymaltose

APPROVED PROFESSIONAL INFORMATION:

SCHEDULING STATUS:

S3

1. NAME OF THE MEDICINE:

TEVIFER 100, 50 mg/ml, solution for injection/infusion.

TEVIFER 500, 50 mg/ml, solution for injection/infusion.

TEVIFER 1 000, 50 mg/ml, solution for injection/infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

One ml of solution contains 50 mg of iron as ferric carboxymaltose.

TEVIFER is supplied as 2 ml, 10 ml and 20 ml solution containing 100 mg, 500 mg and 1 000 mg iron, respectively.

Excipient(s) with known effect:

One ml of solution contains 4,23 mg sodium, see **section 4.4**.

Sugar free.

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM:

Solution for injection/infusion.

A dark brown, non-transparent, aqueous solution.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

TEVIFER is indicated for treatment of iron deficiency in adults when oral iron preparations are ineffective or cannot be used. The diagnosis must be based on laboratory tests.

4.2 Posology and method of administration:

Safety of repeated dose during pregnancy has not been established.

Posology:

Calculation of the cumulative dose:

The adequate cumulative dose of TEVIFER must be calculated for each patient individually and must not be exceeded. For overweight patients, a normal body weight/blood volume relation should be assumed when determining the iron requirement. The dose of TEVIFER is expressed in mg of elemental iron.

The cumulative dose required for haemoglobin restoration and repletion of iron stores is calculated by the following Ganzoni formula:

Cumulative iron deficit [mg] =

body weight [kg] x (target Hb - actual Hb) [g/dL]** x 2,4*** + iron storage depot [mg]*****

** Target Hb for body weight below 35 kg = 13 g/dL respectively 8,1 mmol/L.*

Target Hb for body weight 35 kg and above = 15 g/dL respectively 9,3 mmol/L.

*** To convert Hb [mM] to Hb [g/dL]: multiply Hb [mM] by the factor 1,61145.*

**** Factor 2,4 = 0,0034 x 0,07 x 10000,*

0,0034: iron content of haemoglobin ≙ 0,34 %;

0,07: blood volume ≙ 7 % of body weight;

10 000: conversion factor 1 g/dL =10 000 mg/L.

**** *Depot iron for body weight below 35 kg = 15 mg/kg body weight.*

Depot iron for body weight 35 kg and above = 500 mg.

For patients ≤ 66 kg: the calculated cumulative dose is to be rounded down to the nearest 100 mg.

For patients > 66 kg: the calculated cumulative dose is to be rounded up to the nearest 100 mg.

Patients may continue to require therapy with TEVIFER at the lowest dose necessary to maintain target levels of haemoglobin and other laboratory values of iron storage parameters within acceptable limits.

Maximum tolerated single dose:

The adequate cumulative dose of TEVIFER must be calculated for each patient individually and must not be exceeded.

Since TEVIFER is an alkaline solution, it must never be given via a subcutaneous or intramuscular route. Paravenous leakage at the administration site must be avoided as leakage may cause pain, inflammation, tissue necrosis, sterile abscess or brown discolouration of the skin.

Intravenous bolus injection:

TEVIFER may be administered by intravenous injection up to a maximum single dose of 4 ml (200 mg of iron) per day but not more than three times a week.

Test dose:

Before therapeutic dose is given to a new patient, a test dose of 10 ml to 15 ml (20 mg to 30 mg) of diluted TEVIFER should be given intravenously. If no adverse reaction occurs within 15 minutes, the remaining portion of the initial dose may be given (see *Dilution plan of TEVIFER below*).

Intravenous drip infusion:

TEVIFER may be administered by intravenous infusion up to a maximum single dose of 20 ml of TEVIFER (1 000 mg of iron) but not exceeding 0,3 ml of TEVIFER (15 mg of iron) per kg body weight or the calculated cumulative dose. Do not administer 20 ml (1 000 mg of iron) as an infusion more than once a week.

Paediatric population:

The use of TEVIFER has not been studied in children and is therefore not recommended in children under 18 years.

Method of administration:

TEVIFER must be administered only by the intravenous route as a drip infusion. In a drip infusion, TEVIFER must be diluted only in sterile 0,9 % sodium chloride solution as follows:

Dilution plan of TEVIFER for intravenous drip infusion:

TEVIFER	Iron	Maximum amount of sterile 0,9 % sodium chloride solution	Minimum administration time
2 to < 4 ml	100 to < 200 mg	50 ml	-
4 to < 10 ml	200 to < 500 mg	100 ml	6 minutes
10 to 20 ml	500 to 1 000 mg	250 ml	15 minutes

Note: For stability reasons, dilutions to concentrations less than 2 mg iron/ml are not permissible.

TEVIFER can only be administered as a bolus injection during a haemodialysis session. In this method, direct injection into the venous limb of the dialyser should be used.

TEVIFER must not to be administered by the intramuscular route.

For incompatibilities refer to **section 6.2** and **6.6**.

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

Each vial of TEVIFER is intended for single use only. Any unused product or waste material should be discarded (see **section 6.3**).

4.3 Contraindications:

The use of TEVIFER is contraindicated in cases of:

- known hypersensitivity to ferric carboxymaltose or to any of the excipients as listed in **section 6.1**
- known serious hypersensitivity to other parenteral iron products
- anaemia not attributed to iron deficiency, e.g. other microcytic anaemia
- evidence of iron overload or disturbances in utilisation of iron
- pregnancy in the first trimester.

4.4 Special warnings and precautions for use:

Hypersensitivity reactions:

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 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 such as TEVIFER, in patients with immune or inflammatory conditions (e.g. systemic lupus erythematosus, rheumatoid arthritis).

TEVIFER should only be administered when staff trained to evaluate and manage anaphylactic reactions are 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 TEVIFER administration. 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.

Hepatic or renal impairment:

Parenteral administration of iron must be avoided in patients with hepatic dysfunction, particularly patients with Porphyria Cutanea Tarda where iron overload is a precipitating factor. Careful monitoring of iron status is recommended to avoid iron overload. It is known that the application of ferric carboxymaltose as in TEVIFER may cause transient increases in liver enzymes. In case clinically significant changes in liver enzymes occur, the therapy with TEVIFER should be discontinued, and reinstitution of therapy can be considered once liver enzymes have returned to baseline levels.

No safety data on haemodialysis-dependent chronic kidney disease patients receiving single dose of more than 200 mg iron are available.

Infection:

Parenteral iron must be used with caution in cases of acute or chronic infection, asthma, eczema or atopic allergies. It is recommended that the administration of TEVIFER is stopped in patients with ongoing bacteraemia.

Extravasation:

Caution should be exercised to avoid paravenous leakage when administering TEVIFER. Paravenous leakage of TEVIFER at the injection site may lead to brown discolouration and

irritation of the skin. In case of paravenous leakage, the administration of TEVIFER must be stopped immediately.

Hypophosphataemic osteomalacia:

Symptomatic hypophosphataemia leading to osteomalacia and fractures requiring clinical intervention including surgery has been reported in the post-marketing setting. Patients should be asked to seek medical advice if they experience worsening fatigue with myalgias or bone pain. Serum phosphate should be monitored in patients who receive multiple administrations at higher doses or long-term treatment, and those with existing risk factors for hypophosphataemia. In case of persisting hypophosphataemia, treatment with TEVIFER should be re-evaluated.

Excipients:

TEVIFER contains 4,23 mg sodium per millilitre of undiluted solution, equivalent to 0,2 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

This has to be taken into account in patients on a sodium-controlled diet.

Paediatric population:

The use of TEVIFER has not been studied in children under 18 years of age.

4.5 Interaction with other medicines and other forms of interaction:

The absorption of oral iron is reduced when administered concomitantly with parenteral iron preparations such as TEVIFER.

Therefore, if required, oral iron therapy should not be started for at least 5 days after the last administration of TEVIFER.

Incompatibilities:

The compatibility with containers other than polyethylene and glass is not known (see **section 6.2**). TEVIFER must only be mixed with sterile 0,9 % sodium chloride solution. No other intravenous dilution solutions and therapeutic medicines should be used, as there is the potential for precipitation and/or interaction (see **section 6.6**).

4.6 Fertility, pregnancy and lactation:

Pregnancy:

Safety in pregnancy has not been established. TEVIFER should not be used in the first trimester of pregnancy.

Animal data suggest that iron released from ferric carboxymaltose as in TEVIFER can cross the placental barrier and that its use during pregnancy may influence skeletal development in the foetus.

Breastfeeding:

Safety in lactation has not been established. Clinical studies showed that transfer of iron from ferric carboxymaltose as in TEVIFER to human milk was negligible (≤ 1 %). Based on data from breastfed infants whose mothers received ferric carboxymaltose as contained in TEVIFER, it is unlikely to represent a risk to the nursing child.

Fertility:

There are no data on the effect of TEVIFER on human fertility.

4.7 Effects on ability to drive and use machines:

After the patient received TEVIFER, he/she may feel dizzy, confused or lightheaded.

TEVIFER may impair the ability to drive or operate machines.

4.8 Undesirable effects:

a. Summary of the safety profile:

The most frequently reported undesirable effect is nausea, followed by injection/infusion site reactions, hypophosphataemia, headache, dizziness and hypertension. Injection/infusion site reactions comprise several undesirable effects which individually are less frequent.

The most serious undesirable effect is anaphylactoid/anaphylactic reactions (less frequent); fatalities have been reported. See **section 4.4** for further details.

b. Tabulated list of adverse reactions:

(MedDRA) System Organ Class	**Adverse reaction and frequency**	
Immune system disorders	*Less frequent*	Hypersensitivity, anaphylactoid/ anaphylactic reactions
Metabolism and nutrition disorders	*Frequent*	Hypophosphataemia
Nervous system disorders	*Frequent*	Headache, dizziness
	Less frequent	Paraesthesia
	Unknown frequency	Loss of consciousness

Psychiatric disorders	*Less frequent*	Anxiety
Cardiac disorders	*Less frequent*	Tachycardia
	Unknown frequency	Kounis syndrome
Vascular disorders	*Frequent*	Hypertension
	Less frequent	Hypotension, phlebitis, syncope, presyncope, flushing
Respiratory, thoracic and mediastinal disorders	*Less frequent*	Dyspnoea, bronchospasm
Gastrointestinal disorders	*Frequent*	Nausea, abdominal pain, constipation, diarrhoea
	Less frequent	Vomiting, dyspepsia, flatulence, dysgeusia
Skin and subcutaneous tissue disorders	*Frequent*	Rash
	Less frequent	Pruritus, urticarial erythema, angioedema, pallor, distant skin discolouration
	Unknown frequency	Face oedema

Musculoskeletal and connective tissue disorders	*Less frequent*	Myalgia, back pain, arthralgia, pain in extremity, muscle spasms
	Unknown frequency	Hypophosphataemic osteomalacia
General disorders and administration site conditions	*Frequent*	Injection/infusion site reactions
	Less frequent	Pyrexia, fatigue, chest pain, peripheral oedema, chills, malaise, influenza like illness (whose onset may vary from a few hours to several days)
Investigations	*Frequent*	Alanine aminotransferase increased

	Less frequent	Aspartate aminotransferase increased, gamma-glutamyl transferase increased, blood lactate dehydrogenase increased, blood alkaline phosphatase increased

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. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website.

4.9 Overdose:

Administration of TEVIFER in quantities exceeding the amount needed to correct iron deficit at the time of administration may lead to accumulation of iron in storage sites eventually leading to haemosiderosis. Monitoring of iron parameters such as serum ferritin and transferrin saturation may assist in recognising iron accumulation.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

A 8.3 Erythropoietics (haematinics)

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

Mechanism of action:

Pharmacodynamic effects:

Ferric carboxymaltose solution for injection/infusion contains iron in a stable ferric state as a complex with a carbohydrate polymer designed to release utilisable iron to the iron transport and storage proteins in the body (ferritin and transferrin).

Using positron emission tomography (PET) it was demonstrated that red cell utilisation of ^{59}Fe and ^{52}Fe from ferric carboxymaltose ranged from 61 % to 99 %. Patients with iron deficiency showed utilisation of radio-labelled iron of 91 % to 99 % after 24 days, and patients with renal anaemia showed utilisation of radiolabelled iron of 61 % to 84 % after 24 days.

5.2 Pharmacokinetic properties:

Distribution:

Using positron emission tomography (PET) it was demonstrated that ^{59}Fe and ^{52}Fe from ferric carboxymaltose was rapidly eliminated from the blood, transferred to the bone marrow, and deposited in the liver and spleen.

After administration of a single dose of ferric carboxymaltose of 100 to 1 000 mg of iron in iron deficient patients, maximum iron levels of 37 µg/ml up to 333 µg/ml after 15 minutes to 1,21 hours respectively are obtained. The volume of the central compartment corresponds well to the volume of the plasma (approximately 3 litres).

Elimination:

The iron injected or infused was rapidly cleared from the plasma, the terminal half-life ranged from 7 to 12 hours, the mean residence time (MRT) from 11 to 18 hours. Renal elimination of iron was negligible.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Sodium hydroxide (pH adjuster)

Hydrochloric acid (pH adjuster)

Water for injection

6.2 Incompatibilities:

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

The compatibility with containers other than polyethylene and glass is not known.

6.3 Shelf life:

24 months

Shelf life after first opening of the container:

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 the user.

Shelf life after dilution with sterile 0,9 % m/v sodium chloride solution:

Chemical and physical in-use stability has been demonstrated for 24 hours at 15 to 25 °C.

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 15 to 25 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage:

Store at or below 25 °C.

Store in the original package until required for use.

For storage conditions after reconstitution and dilution of the medicine, see **section 6.3**.

6.5 Nature and contents of container:

TEVIFER solution for injection/infusion 50 mg/ml, 2 ml, 10 ml and 20 ml are packed into colorless, Type I glass vial with bromobutyl rubber stopper and an aluminium cap.

– 2 ml solution containing 100 mg iron. Available in pack sizes of 1, 2 and 5 vials.

– 10 ml solution containing 500 mg iron. Available in pack sizes of 1, 2 and 5 vials.

– 20 ml solution containing 1000 mg iron. Available in a pack size of 1 vial.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling:

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

Each vial of TEVIFER is intended for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

TEVIFER must only be mixed with sterile 0,9 % sodium chloride solution. No other intravenous dilution solutions and therapeutic medicines should be used, as there is the potential for precipitation and/or interaction (see **section 4.5**).

7. HOLDER OF CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd

Maxwell Office Park

Magwa Crescent West

Waterfall City, Midrand

2090

South Africa

8. REGISTRATION NUMBERS:

TEVIFER 100: 57/8.3/0484

TEVIFER 500: 57/8.3/0485

TEVIFER 1000: 57/8.3/0486

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

18 February 2025

10. DATE OF REVISION OF THE TEXT:

To be allocated by SAHPRA