SCHEDULING STATUS

S3

1. **NAME OF MEDICINE:**

   INNOFER 20 mg iron per mL (Solution for injection)

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION:**

   Each 5 ml of **INNOFER** contains 100 mg iron in the form of Iron (III) – Hydroxide Sucrose Complex; 20 mg iron per mL.

   Contains no preservatives.

   “Contains sugar”.

3. **PHARMACEUTICAL FORM**

   Solution for injection

   A homogenous brown liquid filled in 5 ml clear USP Type1 glass ampoules.

4. **CLINICAL PARTICULARS**

4.1 Therapeutic Indications

Severe iron deficiency in adult patients not tolerating or responding to oral iron.

INNOFER is recommended for use only where the indication is definite and confirmed by appropriate investigations.

4.2 Posology and method of administration

Administration:

INNOFER must be administered by a slow intravenous injection, by an intravenous drip infusion or, in patients receiving haemodialysis, into the venous limb of the dialyser (see **Section 4.4**).

INNOFER is a strongly alkaline solution and must never be administered by the subcutaneous or intramuscular route. Paravenous leakage must be avoided because leakage of **INNOFER** at the injection site may lead to pain, inflammation, tissue necrosis, and brown discolouration of the skin.

INNOFER is not suitable for intramuscular use nor for TDI (Total Dose Infusion).

TEST DOSE

Before administration of the first therapeutic dose of INNOFER in a new patient, a test dose of 1 mL to 2,5 mL INNOFER (20 mg to 50 mg iron) should be given by the chosen method of administration (see below). If no adverse reaction occurs within a waiting period of at least 15 minutes after administration, the remaining portion of the initial dose may be given.

Infusion:

The content of one ampoule has to be diluted exclusively in 100 mL of sterile 0,9 % m/V sodium chloride solution, immediately prior to infusion (i.e. 2 ampoules in 200

mL sterile 0,9 % m/V NaCl). The first 25 mg of iron (i.e. 25 mL of solution) should be infused as a test dose over a period of 15 minutes (see above **TEST DOSE**). If no adverse reaction occurs during this time then the remaining portion of the infusion should be given as follows:

- 100 mg iron (5 mL **INNOFER**) in at least 15 minutes
- 200 mg iron (10 mL **INNOFER**) in at least 30 minutes

Intravenous injection:

As an intravenous injection **INNOFER** must be administered slowly at a rate of 1 mL undiluted solution per minute (i.e. 5 minutes per ampoules) not exceeding 2 ampoules **INNOFER** (200 mg iron) per injection. Before administering a slow intravenous injection, a test dose of 1 mL (20 mg of iron) should be injected slowly over a period of 1 to 2 minutes. If no adverse event occurs within 15 minutes of completing the test dose, the remaining portion of the injection may be given.

Injection into dialyser:

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

DOSAGE

Calculation of dosage

Adult<u>s</u> [~~Adult~~] and the elderly

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

Total iron deficit [mg] = body weight [kg] x (target Hb-actual Hb)
[g/dl] x 2,4* + depot iron [mg]

Below 35 kg weight: target Hb = 13 g/dl resp. depot iron = 15 mg/kg body weight

35 kg body weight and above: target Hb = 15 g/dL resp. depot iron = 500 mg

*Factor 2,4 = 0,0034 x 0,07 x 1 000 x 10

where 0,0034 = Iron content of haemoglobin = 0,34 %

0,07 = Blood volume = 7 % of body weight

1 000 = Factor = conversion from g to mg

10 = Factor = conversion from g/dL to g/L

TOTAL NUMBER OF INNOFER AMPOULES TO BE ADMINISTERED				
Body weight kg	Haemoglobin 6 g/dL	Haemoglobin 7,5 g/dL	Haemoglobin 9 g/dL	Haemoglobin 10,5 g/dL
30	9 ,5	8,5	7,5	6,5
35	12,5	11,5	10,0	9,0
40	13,5	12,0	11,0	9,5
45	15	13,0	11,5	10,0
50	16	14,0	12,0	10,5
55	17	15,0	13,0	11,0
60	18	16,0	13,5	11,5
65	19	16,5	14,5	12,0

70	20	17,5	15,0	12,5
75	21	18,5	16,0	13,0
80	22,5	19,5	16,5	13,5
85	23,5	20,5	17,0	14,0
90	24,5	21,5	18,0	14,5

Total ampoules of **INNOFER** to be administered = $\frac{\text{Total iron deficit (mg)}}{100 \text{ mg}}$

The total single dose must not exceed 200 mg of iron given not more than three times per week. If the total necessary dose exceeds the maximum allowed single dose, them the administration has to be split.

Children:

The use of **INNOFER** is not recommended for use in children.

4.3 Contraindications

- Known hypersensitivity to iron mono-, disaccharide complex, **INNOFER** or any of its components.
- Iron overload or disturbances in utilisation of iron (e.g. haemochromatosis, haemosiderosis)**.**
- Anaemia not caused by iron deficiency (e.g. haemolytic anaemias).
- Clinical or biochemical evidence of liver damage.
- Infectious hepatitis
- Acute or chronic infection

- A history of asthma, eczema, other allergic disorders or anaphylactic reactions.
- The safety in lactation and children has not been established.
- The first trimester of pregnancy

4.4 Special warnings and precautions for use

INNOFER has a pH of 11 and must therefore be given strictly by the intravenous route, and the maximum daily dose of 200 mg should not be exceeded. Parenterally administered iron preparations can cause severe and potentially fatal allergic or anaphylactic reactions. Therefore, facilities for cardio-pulmonary resuscitation must be available.

In the event of a serious anaphylactic or allergic reaction, and administration of **INNOFER** must be stopped, intramuscular adrenaline should be administered immediately and other supportive measures initiated in line with the established cardio-pulmonary resuscitation procedures of the clinic or hospital.

Mild allergic reactions should be managed by stopping the administration of **INNOFER** and administering antihistamines.

The risk of hypersensitivity reactions is enhanced for patients with known allergies including medicine allergies and patients with a history of severe asthma, eczema or other atopic allergy: therefore, use in these patients is contraindicated (see section 4.3)

There is also an increased risk of hypersensitivity reactions to parenteral iron complexes, as contained in **INNOFER**, inpatients with immune or inflammatory conditions (e.g. systemic lupus erythematosus, rheumatoid arthritis)

Hypotensive episodes may occur if the injection is administered too rapidly.
Patients with low iron binding capacity and/or folic acid deficiency are particularly at risk of an allergic or anaphylactic reaction. In cases of inadvertent paravenous leakage, and while the needle is still inserted, rinse with a small amount of 0,9 % sodium chloride solution.

Careful monitoring of iron status is recommended to avoid iron overload.
In patients with liver dysfunction, administration of **INNOFER** is not recommended, in particular where iron overload is a precipitating factor and in patients with Porphyria Cutanea Tarda (PCT). **INNOFER** is contraindicated in the presence of clinical or biochemical evidence of liver damage (see section 4.3).

INNOFER should not be administered in combination with oral iron preparations.
INNOFER must not be mixed with other medicines for simultaneous administration. A sterile 0,9 % m/v sodium chloride solution is the only recommended diluent for an infusion

Ampoules should be visually inspected for damage before use and only those with a sediment-free solution may be used. From a microbiological point of view, the product should be used immediately after first opening the container or after dilution with sterile 0,9 % m/v sodium chloride. Residual solvents must be discarded, once the ampoule has been opened.

Symptomatic hypophosphataemia leading to osteomalacia and fractures requiring clinical intervention including surgery has been reported in the post marketing setting.

- Patients should be advised 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 such as vitamin D deficiency, calcium and phosphate malabsorption, secondary hyperparathyroidism, hereditary hemorrhagic telangiectasia, inflammatory bowel disease, and osteoporosis.
- In case of persisting hypophosphataemia, treatment should be re-evaluated.'

INNOFER contains sucrose. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose mal-absorption or sucrase-isomaltase insufficiency should not take **INNOFER**.

4.5 Interaction with other medicines and other forms of interaction

INNOFER should not be administered concomitantly with oral iron preparations, since the absorption of oral preparations is reduced. Oral iron therapy should be started at least 5 days after the last injection of **INNOFER.**

4.6 Fertility, pregnancy and lactation

Pregnancy

INNOFER is recommended for use in the second and third trimester and not for use during the first trimester in pregnancy~~,~~ (see section 4.3).

INNOFER should only be used in pregnant women with severe iron deficiency anaemia; where there is inability to absorb or tolerate adequate amounts of oral iron.

Breast feeding

Safety during lactation has not been established.

Fertility

Safety during fertility has not been established.

4.7 Effects on ability to drive and use machines

When driving or operating machines, it should be taken into account that dizziness or weariness may occur during treatment.

4.8 Undesirable effects

Anaphylactoid reactions are the most serious adverse reactions.

Immune system disorders

Less frequent: Hypersensitivity

Frequency not known: Anaphylactoid/anaphylactic reactions, angioedema

Nervous system disorders*:*

Frequent: Transient taste perversions (in particular metallic taste), dysgeusia.

Less Frequent: Headache; dizziness, paraesthesia, hypoaesthesia, syncope, somnolence

Frequency not known: Depressed level of consciousness, confusional state, loss of consciousness, anxiety, tremor

Cardiac disorders:

Less Frequent: Palpitations.

Frequency not known: Bradycardia, and tachycardia

Vascular disorders

Frequent: Hypotension, hypertension

Less Frequent: Flushing, phlebitis

Frequency not known: Circulatory collapse, thrombophlebitis

Respiratory, thoracic and mediastinal disorders:

Less Frequent: Bronchospasm, dyspnoea.

Renal and urinary disorders:

Less Frequent: Chromaturia

Gastrointestinal disorders*:*

Less Frequent: Nausea; vomiting; abdominal pain; diarrhoea, constipation

Skin and subcutaneous tissue disorders:

Less Frequent: Pruritus; urticaria; rash; exanthema, erythema.

Musculoskeletal, connective tissue and bone disorders*:*

Less Frequent: Muscle cramps, myalgia, arthralgia, pain in extremity, back pain.

Frequency unknown: Hypophosphataemic osteomalacia

General Disorders and administrative site conditions:

Frequent: Injection/infusion site reaction

Less Frequent: Fever, shivering, flushing, chest pain and tightness. Injection site disorders such as superficial phlebitis, burning, swelling, peripheral oedema; fatigue, asthenia, malaise.

Frequency not known: Reduced level of consciousness, lightheaded feeling, confusion, angio-oedema; swelling of joints, hyperhidrosis, back pain, cold sweat, pallor and influenza-like illness.

Investigations:

Less Frequent: Alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyl transferase increased, serum ferritin increased, blood lactate dehydrogenase increased.

4.9 Overdose

Over-dosage can cause acute iron overloading which may manifest itself as hemosiderosis. Particular caution should be exercised to avoid iron overload where anaemia, non-response to treatment, has been incorrectly diagnosed as iron deficiency anaemia.

Overdosage should be treated, if required, with an iron chelating agent.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Class of medicine: Erythropoietics (haematinics), A8.3

The Polynuclear Iron (III) – Hydroxide cores are superficially surrounded by a large number of non-covalently bound sucrose molecules resulting in an over-all complex molecular mass Mw of approximately 43kD. This is sufficiently large to prohibit renal elimination. The resulting complex is stable and does not release ionic iron under physiologic conditions. The iron in the polynuclear cores is bonded in a structure similar to ferritin**.**

5.2 Pharmacokinetic properties

After administering a single intravenous dose of 100 mg **INNOFER** in healthy volunteers, a maximum mean iron level of 538 µmol/L was reached after 10 minutes. The volume of distribution of the central compartment corresponds to the volume of plasma (approximately 3 litres).

The iron injected is quickly cleared from the plasma; the terminal half-life is approximately 6 hours. The volume of distribution at steady state is about 8 litres, which indicates a low iron distribution in the body fluid. Due to the lower stability of Iron (III) – Hydroxide Sucrose Complex in comparison to transferrin, a competitive exchange of iron to transferrin was observed. This results in an iron transport of approximately 31 mg iron/24 hours.

Renal elimination of iron, occurring in the first 4 hours after injection, corresponds to less than 5 % of the total body clearance (approximately 20 ml/minute). After 24 hours the plasma level of iron is reduced to the pre-dose iron levels and about 75 % of the dosage of sucrose is excreted.

5.3 Pre-Clinical 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

Excipients: Water for injections

6.2 Incompatibilities

INNOFER must not be mixed with other medicines. 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

36 months from date of manufacture**.**

6.4 Special Precautions for storage

Store at or below 30 °C in the original carton until removed for use. Protect from light. Do not freeze.

6.5 Nature and contents of container

5 ml clear ampoules, flat based constricted neck of colourless natural glass USP Type 1 with a purple colour snap off in packs of 5 ampoules.

6.6 Special precautions for disposal and other handling

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Innovata Pharmaceuticals Pty LTD

Crownwood Office Park

100 Northern Parkway

Ormonde

Johannesburg

2091

South Africa

8. REGISTRATION NUMBERS

50/8.3/0580

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 MAY 2020

10. DATE OF REVISION OF THE TEXT

19/07/2021