SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Tardyferon® 80 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Ferrous Iron 80mg (as Ferrous sulphate dried 247.25 mg) per coated tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Round, orangish-pink coloured coated tablet.

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
Prevention and treatment of iron deficiency anemia.

4.2. Posology and method of administration
Posology
The usual dosage is:For the treatment of iron deficiency in adults:
1 tablet (equivalent to 80 mg of Fe 2+) per day.
Preventive treatment:
Pregnant women: 1 tablet (equivalent to 80 mg of Fe 2+) per day or every 2 days during the last two trimesters of pregnancy (i.e. from the 4th month onwards).

Duration of treatment:
According to medical judgment.

Method of administration
The tablets should not be sucked, chewed or kept in the mouth, but rather swallowed whole with water.

The tablets must be taken before or during meals depending (except with certain foods mentioned in section 4.5) on the gastrointestinal tolerance.

4.3. Contraindications
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Iron overload, in particular anaemia with normal or high iron levels, such as thalassaemia, refractory anaemia or aplastic anaemia

4.4. Special warnings and precautions for use
Monitoring of efficacy is only useful after 3 months from the beginning of treatment: this should include correction of anaemia (haemoglobin, mean corpuscular volume) and restoration of iron stores (serum ferritin, serum transferrin receptor, and transferrin saturation coefficient).

Iron deficiency associated with inflammatory syndromes does not respond to iron treatment.

Iron treatment must be combined with treatment of the cause wherever possible.

Inhalation of tablets containing ferrous sulphate may cause necrosis of the bronchial mucosa, which can result in coughing, haemoptysis, bronchial stenosis and/or lung infection (even if the tablets were inhaled several days or months prior to the onset of symptoms). Elderly patients and patients with swallowing difficulties may only be treated with tablets containing ferrous sulphate following an in-depth assessment of the risk of inhalation specific to each patient. Alternative pharmaceutical forms should be considered. In the event of suspected inhalation, patients must contact a doctor (see section 4.8).

According to the literature, rare cases of gastrointestinal melanosis (pseudomelanosis/melanosis) have been observed in elderly patients receiving an iron supplement and suffering from chronic kidney disease, diabetes and/or hypertension and treated with several medications for these diseases. This pigmentation may interfere with gastrointestinal surgery and thus should be taken into consideration, especially when surgery is planned. In view of this risk, it is recommended to advise the surgeon of the ongoing iron supplementation (see section 4.8).

Due to the risk of mouth ulceration and tooth discolouration, tablets should not be sucked, chewed or kept in the mouth, but swallowed whole with water.

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, i.e. it is essentially sodium-free.

4.5. Interaction with other medicinal products and other forms of interaction

Inadvisable combinations

- **Iron (salts) (by injection)**

Lipothymia, or even shock, attributed to the rapid release of iron in its complex form and siderophilin saturation.

Combinations to be taken into account

- **Acetohydroxamic acid**

Reduced gastrointestinal absorption of both medicinal products by iron chelation.

Combinations requiring special precautions for use

- **Bictegravir**

Two-thirds decrease in gastrointestinal absorption of bictegravir if both products are administered simultaneously or on an empty stomach.
Bictegravir should be administered at least 2 hours before iron salts or taken together with food.

Bisphosphonates

Reduced gastrointestinal absorption of bisphosphonates due to formation of poorly absorbed complexes.
Do not take iron salts at the same time as bisphosphonates (leave an interval of at least 30 minutes to more than 2 hours, where possible, depending on the bisphosphonate).

- **Cyclins (oral route)**

Reduced gastrointestinal absorption of cyclins and iron.
Do not take iron salts at the same time as cyclins (leave an interval of more than 2 hours where possible).

- **Fluoroquinolones**

Reduced gastrointestinal absorption of fluoroquinolones.
Do not take iron salts at the same time as fluoroquinolones (leave an interval of more than 2 hours where possible).

- **Penicillamine**

Reduced gastrointestinal absorption of penicillamine.
Do not take iron salts at the same time as penicillamine (leave an interval of more than 2 hours where possible).

- **Entacapone**

Reduced gastrointestinal absorption of entacapone and iron caused by chelation of the iron by the entacapone.
Do not take iron salts at the same time as entacapone (leave an interval of more than 2 hours where possible).

- **Thyroid hormones**

Reduced gastrointestinal absorption of thyroid hormones.
Do not take thyroid hormones at the same time as iron (leave an interval of more than 2 hours where possible).

- **Calcium**

Reduced gastrointestinal absorption of iron salts.
Do not take iron salts at meal times or with calcium.

- **Zinc, Strontium**

Reduced gastrointestinal absorption of zinc or strontium caused by iron.
Do not take iron salts at the same time as zinc or strontium (leave an interval of more than 2 hours where possible).

- **Methyldopa, Levodopa**

Reduced gastrointestinal absorption of methyldopa and levodopa.
Do not take iron salts at the same time as methyldopa and levodopa (leave an interval of more than 2 hours where possible).

- **Topical gastrointestinal treatments, antacids, and adsorbents**

Reduced gastrointestinal absorption of iron salts.
As a precaution, do not take topical treatments or antacids at the same time as iron salts (leave an interval of more than 2 hours where possible).

- **Integrase inhibitors**

Reduced gastrointestinal absorption of integrase inhibitors.
Do not take iron salts at the same time as antiretrovirals (leave an interval of more than 2 hours where possible).

- **Trientine**

Reduction in the concentrations of serum iron.
Do not take trientine at the same time as iron salts.

Other forms of interactions

Phytic acids (whole grains), polyphenols (tea, coffee, red wine), calcium (milk, dairy products), and some proteins (eggs) significantly inhibit iron absorption. An interval of at least 2 hours should be left between taking iron salts and these foods.

4.6. Fertility, pregnancy and lactation

Pregnancy

The data on the use of iron supplementation during the 1st trimester of pregnancy are limited but no malformations have been reported. Animal studies do not indicate any reproductive toxicity (see section 5.3). During the second and third trimester, a large quantity of bibliographic data on pregnant women (more than 1000 pregnancies) is available and does not indicate any foeto/neonatal toxicity.

Data from clinical trials show no impact of iron supplementation during pregnancy on birth weight, premature birth and neonatal death.

Consequently, Tardyferon can be used during pregnancy if needed.

Breast-feeding
Iron is present in low quantities in breast milk. Its concentration is not related to the mother's intake. Consequently, no effect is expected on newborns or infants.
Tardyferon can be used during breast-feeding.

Fertility
Studies conducted on animals do not indicate any effect on male or female fertility.

4.7. Effects on ability to drive and use machines
Tardyferon has little or no effect on the ability to drive vehicles and use machine.

4.8. Undesirable effects
The following table presents the undesirable effects observed in seven clinical studies comprising a total of 1,051 patients, 649 of whom were taking Tardyferon, for which a causal relationship with the product cannot be excluded, as well as those observed during the post-marketing experience or in the literature.

The undesirable effects are presented according to their MedDRA System Organ Class and listed below as very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥ 1/10,000, < 1/1,000), very rare (< 1/10,000) or not known (cannot be estimated from the available data).

System organ class	Common (≥ 1/100 < 1/10)	Uncommon (≥ 1/1,000 < 1/100)	Not known (cannot be estimated from the available data)
Immune system disorders			Hypersensitivity
Respiratory, thoracic and mediastinal disorders		Laryngeal oedema	*Pulmonary necrosis, *Pulmonary granuloma, *Bronchostenosis *Pharyngeal ulceration
Gastrointestinal disorders	Constipation, Diarrhoea, Abdominal distension, Abdominal pain, alteration in faeces colour, Nausea	Abnormal faeces, Dyspepsia, Vomiting, Gastritis	*Oesophageal lesions *Oesophageal ulceration **Tooth discolouration, mouth ulceration, Gastrointestinal melanosis (see section 4.4), *** Gastric haemorrhage Gastric ulcer ***Haemorrhagic gastric ulcer *** Erosive gastritis
Skin and subcutaneous tissue disorders		Pruritus, Erythematous rash	Urticaria

* Patients, particularly elderly patients and patients with swallowing difficulties, may also be at risk of oesophageal lesions (oesophageal ulceration), throat ulcers, bronchial granulomas and/or bronchial necrosis, which can cause bronchostenosis in the event of inhalation of tablets containing ferrous sulphate (see section 4.4).

** Tooth discolouration and mouth ulceration: due to incorrect administration, when the tablets are chewed, sucked or kept in the mouth.

***According to the literature, serious cases of gastric ulcer and gastric haemorrhage have been reported even at therapeutic doses in patients treated with iron sulphate tablets.

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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form at http://sideeffects.health.gov.il
In addition, you can report to Padagis via the following address: Padagis.co.il

4.9. Overdose

Cases of overdose with iron salts have been reported, particularly in children. The risk of overdose-related toxicity begins at a 20 mg/kg dose of elemental iron and increases from 60 mg/kg.

Symptoms

Iron poisoning develops in 5 successive symptomatic stages:

- A gastrointestinal stage including signs of irritation of the gastrointestinal mucosa combined, in most cases, with abdominal pain, nausea, vomiting, diarrhoea and bleeding (haematemesis, melaena) which may lead to necrosis.
- A clinical latency stage with stabilisation or regression of gastrointestinal symptoms.
- A systemic stage with onset of anion gap metabolic acidosis, coagulopathy and haemodynamic instability (hypovolaemia, hypotension) with hypoperfusion of organs (acute kidney injury, lethargy and coma often convulsive) which may lead to shock.
- A hepatotoxicity stage which may range from elevated transaminases to coagulopathy and hepatic encephalopathy.
- And even when the symptoms of poisoning have subsided, gastrointestinal stenosis related to gastrointestinal wound-healing is possible.
  Monitoring of the warning signs is therefore recommended.

  Diagnosis depends primarily on clinical symptoms and is supported by a high serum iron level and, where necessary, an abdominal X-ray (confirming the presence of tablets in the gastrointestinal tract).

Treatment

Treatment should be initiated as soon as possible:
• Symptomatic treatment: The patient should be monitored closely. Shock, dehydration and acid-base anomalies should be treated according to the current practice in

specialised units (maintenance of the patient's breathing, blood volume, water and electrolyte balance and diuresis of the patient).
• Gastrointestinal decontamination: This may be considered in a specialised environment in certain specific situations but should not be used routinely. In particular, intestinal irrigation with polyethylene glycol solution may be considered if there is a significant quantity of iron tablets or concretions in the gastrointestinal tract visible by X-ray in a patient showing symptoms. It should then be performed until the wastewater is clear.
• Iron chelation therapy: Depending on serum iron concentrations and the severity or persistence of symptoms, the use of a chelating agent is recommended if the poisoning is major. The primary therapeutic protocol is deferoxamine.
For more detailed information, see the SmPC (summary of product characteristics) for deferoxamine.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: ANTIANAEMIC PREPARATIONS – IRON PREPARATIONS – ATC code: B03AA07

Ferrous iron supplementation.
Iron is an essential mineral nutrient which plays a key physiological role and is required for many functions such as the transport of oxygen, production of ATP, synthesis of DNA and transport of electrons.

Mechanism of action:
Iron is the central atom of haem. It is a component of haemoglobin and is also essential for erythropoiesis.

Pharmacodynamic effects:
Iron is different from other minerals due to the fact that its balance in the human body is only regulated by its absorption, as there is no physiological excretion mechanism. The ingestion of ferrous sulphate (FeSO4) is facilitated by the iron transporter (DMT1) in the proximal part of the small intestine (duodenum and proximal jejunum).

5.2. Pharmacokinetic properties

Absorption
Iron absorption is an active process taking place essentially in the duodenum and the proximal jejunum.

The combination of ferrous sulphate and excipients allows iron to be released in a continuous and progressive manner. Absorption is increased when iron reserves are depleted and reduced when iron reserves are sufficient.

Iron absorption may be impaired by certain foods or beverages and with the concomitant administration of certain medicinal products (see section 4.5).

Distribution
In the body, iron reserves are mainly found in the bone marrow (erythroblasts), erythrocytes, liver and spleen. In the blood, iron is transported by transferrin mainly to the bone marrow where it is incorporated into haemoglobin.

Biotransformation
Iron is a metal ion which is not metabolised.

Elimination
There is no active excretion mechanism for iron.

Mean iron excretion in healthy subjects is estimated at 0.8–1 mg/day.
Iron is mainly eliminated via the gastrointestinal tract (desquamation of enterocytes, degradation of haem from the extravasation of red blood cells), the urogenital tract and the skin. Any excess iron in the digestive system is eliminated in the faeces.

5.3. Preclinical safety data

The preclinical data from conventional studies on safety pharmacology, repeated dose toxicity, genetic toxicity, carcinogenesis and reproductive function and development reveals no particular risk for humans at the proposed doses.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Core: Cellulose microcrystalline, maltodextrin, ammonio methacrylate copolymer type B, glycerol dibehenate, talc, ammonio methacrylate copolymer type A, triethylcitrate.
Film coating:Sepifilm LP010, titanium dioxide, triethylcitrate, red iron oxide, yellow iron oxide.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4. Special precautions for storage

Store below 30ºC

6.5. Nature and contents of container

30 coated tablets in blister packs (PVC/PVDC/Aluminium)

6.6. Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Padagis Israel Agencies Ltd.
1 Rakefet St., Shoham

8. MARKETING AUTHORISATION NUMBER

13566.31400
Revised in April 2023..

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