SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
TARDYFERON

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Ferrous sulphate 247.25 mg per film-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), or as according to medical judgment.

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 on the patient's 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
Warnings

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, brown-black pigmentation of the gastrointestinal mucosa (pseudomelanosis/melanosis) has been observed rarely in elderly patients who receive an iron supplement and who suffer from chronic kidney disease, diabetes and/or hypertension. This pigmentation may interfere with gastrointestinal surgery and thus should be taken into consideration, especially when surgery is planned. Therefore, it is recommended to advise the surgeon of the ongoing iron supplementation, considering such risk (see section 4.8).

Precautions for use

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

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 transferrin saturation.

Combinations to be taken into account

- **Acetohydroxamic acid**

Reduced gastrointestinal absorption of both medicinal products by iron chelation.

Combinations subject to precautions for use

- **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 caused by calcium.
Do not take iron salts at meal times or with calcium.

- **Zinc, Strontium**

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

- **Methyldopa, Levodopa**

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

- **Magnesium, aluminium and calcium salts, oxides and hydroxides (gastrointestinal mineral preparations)**

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

4.6. Fertility, pregnancy and lactation

Pregnancy

There is limited data available on the use of iron in the first trimester of pregnancy for assessing the risk of malformation.

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

Animal studies do not indicate any reproductive toxicity (see section 5.3).
Consequently, the use of iron salts will only be considered during pregnancy when necessary.

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 may 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 machinery.

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 during the post-marketing experiment 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).

	Common (≥ 1/100 < 1/10)	**Uncommon** (≥ 1/1,000 < 1/100)	**Not known** (cannot be estimated from the available data)

Immune system disorders			Hypersensitivity, urticaria
Respiratory, thoracic and mediastinal disorders		Laryngeal oedema	**Pulmonary necrosis, **Pulmonary granuloma, **Bronchial stenosis, **Pharyngeal ulceration,
Gastrointestinal disorders	Constipation, diarrhoea, abdominal distension, abdominal pain alteration in stool colour, nausea	Abnormal stools, dyspepsia, vomiting, gastritis	*Tooth discolouration, mouth ulceration, Gastrointestinal melanosis, **Oesophageal injury, **Oesophageal ulceration
Skin and subcutaneous tissue disorders		Pruritus, erythematous rash	

* Tooth discolouration and mouth ulceration: due to incorrect administration, when the tablets are chewed, sucked or kept in the mouth.
** 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 bronchial stenosis in the event of inhalation of tablets containing ferrous sulphate (see section 4.4).

Other special groups
According to the literature, brown-black pigmentation of the gastrointestinal mucosa (pseudomelanosis/melanosis) has been observed rarely in elderly patients who receive an iron supplement and who suffer from chronic kidney disease, diabetes and/or hypertension. This pigmentation may interfere with gastrointestinal surgery (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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 Perrigo via the following address: www.perrigo-pharma.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.

Iron poisoning develops in five 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 improvement or even disappearance 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 often convulsive coma) which may lead to shock.
- A hepatotoxicity stage which may range from elevated transaminases to coagulopathy and hepatic encephalopathy.

And in cases not involving poisoning, 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 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, fluid and electrolyte balance and diuresis).
• Gastrointestinal decontamination: This may be considered in a specialised environment in certain specific situations but should not be used routinely. In particular, colonic 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 in cases of major poisoning. The primary therapeutic protocol is deferoxamine.
For more detailed information, see the Prescribing Information for deferoxamine.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: ANTIANEMIC 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 ($FeSO_4$) 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 excipients

Cellulose microcrystalline, maltodextrin, ammonio methacrylate copolymer type B, glycerol dibehenate, talc, ammonio methacrylate copolymer type A, triethylcitrate.

Coating excipients

Sepifilm LP010, titanium dioxide, triethylcitrate, red iron oxide, yellow iron oxide, water.

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 film-coated tablets in blister packs (PVC/PVDC/Aluminium)

6.6. Special precautions for disposal and other handling
No special requirements.

7. MARKETING AUTHORISATION HOLDER
Perrigo Israel Agencies Ltd.
1 Rakefet St., Shoham

8. MANUFACTURER
Pierre Fabre Medicament Production
45, Place Abel Gance, 92100 Boulogne, France

9. MARKETING AUTHORISATION NUMBER
135-66-31400-00

Revised on September 2020