MODULE 1	**REGIONAL ADMINISTRATIVE INFORMATION**	***CONFIDENTIAL***
MODULE 1.3	**PRODUCT INFORMATION**	
MODULE 1.3.2	**SUMMARY OF PRODUCT CHARACTERISTICS (SPC)**	

MODULE 1

REGIONAL ADMINISTRATIVE INFORMATION

1.3 PRODUCT INFORMATION

1.3.1 Summary of Product Characteristics (SPC)

MODULE 1	**REGIONAL ADMINISTRATIVE INFORMATION**	***CONFIDENTIAL***
MODULE 1.3	**PRODUCT INFORMATION**	
MODULE 1.3.2	**SUMMARY OF PRODUCT CHARACTERISTICS (SPC)**	

1.3.1 Summary of product characteristics (SPC).

Summary of product characteristics is presented on the following pages.

FEROSE 50MG/5ML SYRUP

1. Name of the medicinal product

Ferose 50mg/5ml Syrup.

2. Qualitative and quantitative composition

Each 5ml Ferose Syrup contains:

50mg Iron as Iron(III)-hydroxide polymaltose complex

Excipients:

~~Each 5ml of syrup contains:~~

Sucrose ~~- 1.0 g~~

Sorbitol Solution 70% Non-Cryst~~. 2.0 g~~

Methylparahydroxybenzoate - ~~2.915 mg~~

Propyl-Parahydroxybenzoate - 0~~.8325 mg~~

Ethanol ~~- 16.25mg~~

3. Pharmaceutical form

Syrup.

4. Clinical particulars

4.1 Therapeutic indications

Treatment of iron deficiency without anaemia (latent iron deficiency) and iron deficiency with anaemia (manifest iron deficiency). The iron deficiency and its degree must be diagnostically confirmed by suitable laboratory analyses.

4.2 Posology and method of administration

	Daily dose of iron in mg	
	Iron deficiency with anaemia	**Iron deficiency without anaemia**
Infants aged up to 1 year	25-50 mg	15-25 mg
Children (aged 1-12 years)	50-100 mg	25-50 mg

Adolescents aged over 12 years and adults	100-300 mg	50-100 mg

Iron (mg) pharmaceutical form	**2.5 mg**	**5 mg**	**10 mg**	**15 mg**	**25 mg**
Syrup in mL	-	-	-	-	2.5

Iron (mg) pharmaceutical form	**50 mg**	**100 mg**	**200 mg**	**300 mg**
Syrup in mL	5	10	20	30

The daily dose can be divided into individual doses or administered all at once.

The Ferose preparations should be taken with or directly after meals.

Ferose syrup can be mixed with fruit or vegetable juices or with bottle feed.

The slight discolouration does not impair the effect or the taste.

Ferose syrup is to be used and administered at the recommended doses of iron for children aged under 12 years.

The dosage and duration of treatment depend on the degree of the iron deficit. In the case of manifest iron deficiency with anaemia, treatment until the haemoglobin value has normalised lasts an average of 3-5 months. Treatment is then continued with treatment at the respective dose for latent iron deficiency without anaemia for several weeks to fill up the iron stores. Treatment of latent iron deficiency without anaemia lasts around 1-2 months.

4.3 Contraindications

- Known hypersensitivity to or intolerance of the active substance iron(III) hydroxide polymaltose complex or one of the excipients,
- Iron overload (e.g. haemochromatosis, haemosiderosis),
- Iron metabolism disorders (lead anaemia, sideroachrestic anaemia, thalassaemia),
- Any anaemia not caused by iron deficiency (e.g. haemolytic anaemia or megaloblastic anaemia caused by vitamin B12 deficiency).
-

4.4 Special warnings and precautions for use

Anaemias should always be treated under the supervision of a doctor.
If therapeutic success (increase in haemoglobin by about 2-3 g/dL after 3 weeks) is not achieved, treatment should be reconsidered.

Caution is recommended in patients who receive repeated blood transfusions, as there is a supply of iron with erythrocytes, which can lead to iron overload.

Treatment with Ferose can cause dark discolouration of the faeces (stool) but this has no clinical significance.
Infections or tumours can cause anaemia. As oral iron can be utilised only after the primary disease has been treated, a benefit/risk analysis is indicated.
1 mL of Ferose syrup contains 1 mg of sodium. This corresponds to 0.05% of the WHO-recommended maximum daily intake of 2 g of sodium for adults.
1 mL Ferose syrup contains 0.28 mg of sorbitol. Sorbitol can cause gastrointestinal disorders and has a slight laxative effect. Patients with hereditary fructose intolerance (HFI) should not take/receive this medicinal product.
1 mL of Ferose syrup contains 200 mg of sucrose. Diabetes patients must take this into account. Sucrose can be harmful to the teeth.
Ferose syrup contains small quantities of ethanol (alcohol) of less than 100 mg per 30 mL (maximum daily dose).
Ferose syrup contains methyl hydroxybenzoate (E218) and propyl hydroxybenzoate (E216). These can cause allergic reactions, even delayed reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions of the iron(III) hydroxide polymaltose complex with tetracycline or aluminium hydroxide were investigated in three human studies (cross-over design, 22 patients per study). No significant reduction in the absorption of tetracycline was shown. The plasma concentration of tetracycline did not fall below the level necessary for efficacy. The absorption of iron from iron(III) hydroxide polymaltose complex was not reduced by aluminium hydroxide and

tetracycline. The iron(III) hydroxide polymaltose complex can therefore also be administered at the same time as tetracyclines or other phenolic compounds, as well as aluminium hydroxide.

Studies in rats with tetracycline, aluminium hydroxide, acetylsalicylate, sulfasalazine, calcium carbonate, calcium acetate, calcium phosphate in combination with vitamin D3, bromazepam, magnesium aspartate, D-penicillinamine, methyldopa, paracetamol and auranofin have not shown any interactions with the iron(III) hydroxide polymaltose complex.

There were also no interactions of the iron(III) hydroxide polymaltose complex with food components, such as phytic acid, oxalic acid, tannin, sodium alginate, choline and choline salts, vitamin A, vitamin D3 and vitamin E, soy oil and soy flour observed in in-vitro studies. These results indicate that iron(III) hydroxide polymaltose complex can be taken during or immediately after food intake.

The haemoccult test (selective for Hb) for the detection of occult blood is not affected; the therapy therefore must not be interrupted.

The concomitant administration of parenteral iron preparations and Ferose is not indicated as the absorption of the oral iron preparation would be massively inhibited and parenteral iron preparations may only be used if oral treatment is not suitable.

4.6 Fertility, pregnancy and lactation

Clinical data of exposed pregnancies exhibited no undesirable effects on pregnancy or on the health of the foetus or newborn infant (see Properties/Effects). Data from epidemiological studies is not available. Animal studies have not shown any direct or indirect toxicity affecting pregnancy, embryo development or development of the foetus. However, care should be taken when taking this medicinal product during pregnancy.

Human milk naturally contains iron bound to lactoferrin. It is not known how much iron from the iron(III) hydroxide polymaltose complex passes into human milk. It is unlikely that taking Ferose products could cause undesirable effects in the breast-fed infant when taken by the breast-feeding mother. Ferose preparations should only be taken during pregnancy and lactation after consulting a doctor.

4.7 Effects on ability to drive and use machines

No relevant studies have been performed. However, it is unlikely that Ferose has any effect on the ability to drive and use machines.

4.8 Undesirable effects

The frequency of the undesirable effects described below is classified into very common (≥ 1/10), common (< 1/10 to ≥ 1/100) or uncommon (< 1/100 to ≥ 1/1,000).

The safety and tolerability of Ferose were assessed in a meta-analysis of 24 publications or clinical trial reports with a total number of 1473 exposed patients. The most significant adverse drug reactions reported by these trials occurred in 4 system organ classes (see below). Stool discolouration is a well known adverse drug reaction of oral iron preparations but it is not considered clinically relevant and is often not reported. Other commonly observed undesirable effects were gastrointestinal disorders (nausea, constipation, diarrhoea and abdominal pain).

~~*Immune system*~~

~~Very rare: allergic reactions~~

Gastrointestinal disorders

Very common: discoloured faeces

Common: Diarrhoea, nausea, abdominal pain (including: abdominal pain, dyspepsia, epigastric discomfort, abdominal distension), constipation.

Uncommon: Vomiting (including: vomiting, regurgitation), teeth discolouration, gastritis.

Skin and subcutaneous tissue disorders

Uncommon: pruritus, rash (including: rash, macular rash, bullous rash)**, urticaria**, erythema**.

Nervous system disorders

Uncommon: headache.

Musculoskeletal and connective tissue disorders

Rare: Muscle spasms (including: involuntary muscle contraction, tremor), myalgia.

* Stool discolourations were reported in the meta-analysis at a lower frequency but they are generally a well known adverse drug effect of an oral iron therapy. For this reason, stool discolouration was classified under very common undesirable effects.

** Events came from spontaneous reports after market introduction, with an estimated incidence of <1/491 patients (upper limit of 95% confidence interval).

To report any side effect(s):

- The National Pharmacovigilance and Drug Safety Centre (NPC)
- SFDA call center: 19999
- E-mail: npc.drug@sfda.gov.sa
- Website: https://ade.sfda.gov.sa

4.9 Overdose

In the case of overdoses, an intoxication or iron overload is unlikely due to the low toxicity of the iron(III) hydroxide polymaltose complex (in mice and rats, the 50% lethal dose (LD_{50}) is > 2000 mg Fe/kg of body weight) and the expected saturation of iron uptake. No cases of accidental poisoning with fatal outcome are known.

5. Pharmacological properties

5.1 Pharmacodynamic properties

ATC code

B03AB05

Mechanism of action

The polynuclear iron(III) hydroxide core in IPC is surrounded at its surface by a number of non-covalently bound polymaltose molecules, which leads to an average total molecular weight of around 50 kDa. The polynuclear iron core of IPC has a structure similar to that of the physiological iron storage protein ferritin. IPC is a stable complex and releases no large quantities of iron under physiological conditions. Due to its size, the magnitude of IPC diffusion taking place through the mucosa is around 40 times less than in most water-soluble iron(II) salts present in aqueous solution as a hexaaqua-iron(II) complex. Iron is absorbed in the intestines from IPC through an active mechanism.

Pharmacodynamics

The iron absorbed is bound to transferrin and is used for Hb synthesis in the bone marrow or stored primarily in the liver bound to ferritin.

Clinical Efficacy

The efficacy of Ferose compared to a placebo or similar preparations with different iron formulations in terms of normalising haemoglobin values and replenishing iron stores has been demonstrated in numerous clinical studies in infants, children, adolescents and adults. Both solid and liquid galenic forms of IPC were used in these studies. The primary goal of an oral iron replacement is to maintain the body’s own iron stores within normal limit values (to prevent an iron deficiency, e.g. in case of increased requirements), replenish iron stores or correct existing iron deficiency anaemia.

Clinical studies in adults

A total of 11 controlled clinical studies have been carried out with IPC mono-preparations in comparison with a placebo and/or oral iron(II) preparations.

A total of more than 900 patients were involved, and approximately 500 of these patients received IPC mono-preparations. The patient population studied demonstrated no relevant differences in haematological and iron parameters (haemoglobin (Hb), mean red blood cell haemoglobin (MCV), serum ferritin) at the start of treatment. The oral iron replacement with IPC at a dose of 100–200 mg iron/day for several weeks up to a maximum of 6 months demonstrated a clinically relevant increase in iron and haematological parameters at the end of treatment compared to those at the start of treatment. The improvement in haematological parameters (Hb, MCV, serum ferritin) after a 12-week treatment with IPC was comparable to treatment with iron(II) sulphate.

The efficacy of IPC compared to iron(II) sulphate was investigated on the basis of a meta-analysis of 6 prospective, randomised clinical studies in adult patients with iron deficiency anaemia. The total number of patients included in the study was 557; 319 patients received IPC and 238 patients iron(II) sulphate. The pooled mean haemoglobin values at the start of treatment were 10.35 ±0.92 g/dL (IPC) and 10.20 ±0.93 g/dL (iron(II) sulphate). After an average treatment period of 8 to 13 weeks with equivalent posology, mean haemoglobin values were determined 12.13 ±1.19 g/dL (IPC) and 11.94 ±1.84 g/dL (iron(II) sulphate), p=0.93increases in haemoglobin were greater after a longer treatment duration for both iron formulations.

Clinical studies in children and adolescents

The use of Ferose in children and adolescents (18 years old or younger) was investigated in a number of clinical studies involving over 1000 patients. The efficacy of Ferose in terms of improving iron values compared to the placebo or comparable preparations with different iron formulations was thereby confirmed.

5.2 Pharmacokinetic properties

Absorption

Studies with radio-labelled IPC show a good correlation between iron absorption and build-up of iron in haemoglobin. The relative absorption of iron correlates with the degree of iron deficiency (i.e. the greater the iron deficiency, the higher the iron absorption). In contrast to iron(II) salts, it was determined that food had no negative effect on the bioavailability of iron from Ferose: significantly increased bioavailability of iron with concomitant

ingestion of food was demonstrated in a clinical study, while three other studies showed a positive trend but no clinically significant effects.

Elimination

Iron that is not absorbed is eliminated in the faeces.

5.3 Preclinical safety data

Non-clinical data obtained for IPC does not reveal any special hazards for humans based on conventional studies of individual dose toxicity and repeated dose toxicity, genotoxicity or reproduction and development toxicity.

Other information

The LD_{50} of IPC, which was determined in animal trials with mice and rats, was higher than an orally administered dose of 2,000 mg of iron per kg of body weight.

6. Pharmaceutical particulars

6.1 List of excipients

Each 100ml syrup contains:

Excipients	**Quantity (g)**
Sucrose Granular	20.00
Sorbitol Solution 70% Non-Cryst.	40.00
Methyl 4-Hydroxybenzoate	0.0583
Propyl 4-Hydroxybenzoate	0.0167
Ethanol 96%	0.3250
Cream Essence	0.30
Sodium Hydroxide Solution	-
Purified Water (q.s to)	100ml

6.2 Incompatibilities

Not Applicable.

6.3 Shelf life

36Months/3Years

6.4 Special precautions for storage

Store below 25° C and keep in the original packaging.

6.5 Nature and contents of container
100/pack
100ml Amber glass bottle with white child-resistant cap and tamper evident ring

6.6 Special precautions for disposal and other handling
No Special Disposal

7. Marketing authorization holder and Manufacturer

SPIMACO
Al-Qassim Pharmaceutical Plant
Saudi Pharmaceutical Industries &
Medical Appliances Corporation.
Saudi Arabia

8. Marketing authorization number(s)

9. Date of first authorization/renewal of the authorization

10. Date of revision of the text
May 2021.