SUMMARY OF PRODUCT CHARACTERISTICS

OROFER CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

OROFER CAPSULES

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains:

Iron (III) Hydroxide Polymaltose Complex equivalent to

Elemental iron 100 mg.

Folic acid 550 mcg.

3. PHARMACEUTICAL FORM

Size "2" Hard gelatin capsules with scarlet coloured cap & body, imprinted in white ink with, Orofer" on cap & body filled with dark brown powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Orofer capsule is indicated in the treatment of iron deficiency anemia during pregnancy, lactation, and in anemia which is due to post-partum haemorrhage.

It is also indicated in the prevention of iron deficiency anemia.

4.2 Posology and method of administration

Dosage and duration of therapy are dependent upon the extent of iron deficiency.

Treatment of iron deficiency anemia: 1 capsule to be taken orally twice daily

Prevention of iron deficiency anemia: 1 capsule to be taken orally once daily.

In cases of iron deficiency, the therapy takes about 3-5 months until normalization of the hemoglobin value is achieved. Afterwards, the therapy should be continued for several weeks to replenish the iron stores.

Children and adolescents

There are no data on the use of iron hydroxide polymaltose complex in children and adolescents aged 12 years and younger, and therefore it is not recommended.

4.3 Contraindications

- Known hypersensitivity or intolerance to the active ingredients or to any of the excipients.
- Iron overload (e.g hemochromatosis, hemosiderosis)
- disturbances in iron utilization (lead anemia, sideroblastic anemia, thalassemia)
- all anemias not caused by iron deficiency (e.g hemolytic anemia or megaloblastic anemia due to vitamin B12 deficiency).

4.4 Special warnings and precautions for use

Anemia should always be treated under medical supervision.

If the therapy does not succeed (hemoglobin increases by about 2-3 g/dl after 3 weeks), the treatment should be reconsidered.

Orofer capsules contain folic acid and can mask a vitamin B12 deficiency. Due to the risk of irreversible neurological disorders, a possible vitamin B12 deficiency should be excluded in anemic patients before starting therapy.

During the treatment with iron hydroxide polymatose, dark discolouration of the faeces (stool) may occur, however this is not of clinical relevance.

Caution should be exercised in patients who receive repeated blood transfusions, since erythrocytes also supply iron, which can lead to iron overload. Infections or tumors may cause anemia. Since iron can be utilized only after correcting the primary disease, a benefit/risk evaluation is advisable.

Orofer capsules contains lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine

4.5 Interaction with other medicinal products and other forms of Interaction

Interactions of Iron (III) Hydroxide Polymaltose Complex (IPC) with tetracycline or aluminium hydroxide were investigated in three human studies. No significant reduction in the absorption of tetracycline was observed. The plasma tetracycline concentration did not fall below the minimum inhibitory concentration level necessary for bacteriostasis. Iron absorption from IPC was not reduced by aluminium hydroxide

and tetracycline. IPC can therefore also be administered simultaneously with tetracyclines or other phenolic compounds and with 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-penicillamine, methyldopa, paracetamol and auranofin have not shown any interaction with iron (III) hydroxide polymaltose complex.

In addition, no interactions of iron (III) hydroxide polymaltose complex with food constituents such as phytic acid, oxalic acid, tannin, sodium alginate, choline and choline salts, vitamin A, vitamin D3 and vitamin E, soya oil and soya flour were observed in *in vitro* studies. These results suggest that iron hydroxide polymaltose complex can be taken during or immediately after food intake.

The hemoccult test (selective for Hb) for the detection of occult blood is not impaired; and therefore, there is no need to interrupt the therapy.

The simultaneous administration of parenteral iron preparations and iron hydroxide polymaltose complex is not indicated since it would reduce the absorption of the oral iron preparation.

Folic acid could increase phenytoin metabolism, leading to lower serum phenytoin concentrations, especially in folate deficient patients. Some patients may experience an increased frequency of epileptic seizures. Patients who take phenytoin or other antiepileptics/anticonvulsants should consult a doctor before taking a folic acid supplement.
There are reports that concomitant administration of chloramphenicol and folic acid in patients with folic acid deficiency may reduce the hematopoietic response to folic acid. Although the importance and mechanism of this interaction is unclear, the hematopoietic response to folic acid should be carefully monitored in patients receiving both medicines at the same time.

4.6 Pregnancy and lactation

Pregnancy

Orofer capsules can be used in pregnancy and lactation.

Clinical data from exposed pregnant women showed no adverse effects on pregnancy or the health of the fetus or new-born. There is no experience from epidemiological studies. Studies in animals have not shown reproductive toxicity. As a precautionary measure, iron hydroxide polymaltose complex should only be taken after consulting a medical doctor.

Breast-feeding

It is not known whether iron from the iron (III) hydroxide polymaltose complex passes into breast milk. Human breast milk naturally contains iron, which is bound to

lactoferrin. As a precautionary measure, iron hydroxide polymaltose complex should only be taken during breastfeeding after consulting a medical practitioner.

4.7 Effects on ability to drive and use machines:

No relevant studies were undertaken. However, iron hydroxide polymaltose complex is unlikely to have any effect on the ability to drive and use machines.

4.8 Undesirable effects:

The frequency of the side effects described below is divided into very common (≥1/10), common (<1/10 to ≥1/100), uncommon (<1/100 to ≥1/1000) or rare (<1/1000).

The safety and tolerability of iron hydroxide polymaltose complex has been evaluated in a meta-analysis of 24 publications or clinical study reports encompassing total number of 1473 exposed patients. The principal adverse drug side reaction reported in these trials occurred in 4 system organ classes (see below).

Discoloured faeces are a well-known adverse drug reaction of oral iron medications, but this is considered of no clinical relevance and is underreported. Other commonly seen side effects were gastrointestinal disorders (nausea, constipation, diarrhea and abdominal pain).

System Organ Class	Frequency	Adverse event
Gastrointestinal disorders	Very common	faeces discoloration *.
	Common	diarrhea
		nausea
		abdominal pain (including abdominal pain, dyspepsia, epigastric discomfort, abdominal distension)
		constipation
	Uncommon	Vomiting (including vomiting, regurgitation), gastritis.

		tooth discoloration
		gastritis
Skin and subcutaneous Tissue disorders	Uncommon	pruritus
		rash (including rash, macular rash, blistered rash) **
		urticaria **
		erythema **
Nervous System Disorders	Uncommon	headache
Musculoskeletal and Connective Tissue Disorders	Rare	muscle spasms (including involuntary muscle contraction, tremor),
		myalgia

* Faeces discoloration has been reported with less frequency in the meta-analysis but is a well-known drug-related effect of oral iron therapy in general. Therefore, faeces discoloration was allocated as one of the most common side effects.

** Events come from spontaneous post-marketing reports, estimated incidence <1/491 patients (upper limit of 95% confidence interval)

4.9 Overdose

In case of overdoses, intoxication or iron accumulation are unlikely due to the low toxicity of iron (III) hydroxide polymaltose complex [in mice or rats, the 50% lethal dose (LD50) > 2000 mg Fe/Kg body weight] and the expected saturation of the iron intake is unlikely. There are no known cases of accidental fatal poisoning.

There are reports that an excessive dose of folic acid may cause changes in the central nervous system (namely, mood disorders, changes in sleep patterns, irritability and hyperactivity), nausea, abdominal distension and flatulence.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: B03AD04

Mechanism of action

In the IPC, the polynuclear iron (III) hydroxide core is superficially surrounded by a number of non-covalently bound polymaltose molecules, which leads to an average total molecular weight of approximately 50kDa. IPC is a stable complex and does not release large amounts of iron under physiological conditions. The polynuclear iron core of the IPC has a structure similar to the physiological iron storage protein ferritin. Because of its size, the extent of diffusion of IPC through the membrane of the mucosa is about 40 times less than in most water-soluble iron (II) salts, existing in aqueous solution as hexaqua-iron (II) ion complex. Iron from IPC is taken up in the gut via an active mechanism.

Folic acid (folate) belongs to the group of B vitamins. It is a precursor to tetrahydrofolate, a coenzyme that is involved in various metabolic processes, including the biosynthesis of purines and thymidylates of nucleic acids. Folic acid is required for nucleoprotein synthesis and to maintain normal erythropoiesis.

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

Folic acid is the precursor of tetrahydrofolic acid which is active and acts as a co-factor for 1-carbon transfer reactions in the biosynthesis of purines and thymidylates of nucleic acids.

Clinical data

During pregnancy there is an increased iron requirement of approximately 0.8 mg/day in the first trimester, up to over 6 mg/day in the third trimester of pregnancy. In addition, there is an increased need for folic acid, especially during pregnancy. Decreased folic acid levels can lead to deficiency symptoms in both mothers (anemia, peripheral neuropathies) and fetus (congenital neural tube defects).

Clinical studies have been carried out in pregnant women to investigate the safety and efficacy in the treatment of iron deficiency with and without anemia, and to prevent iron and folic acid deficiency by treating IPC in combination with folic acid. Changes in haematological parameters were compared with the treatment of IPC in a dose of 100 mg - 300 mg iron/day in connection with 0.35 mg folic acid / day in comparison to iron (II) sulphate standard preparations with and without folic acid. One study examined the effectiveness of IPC with the addition of a folic acid supplement compared to an intravenous iron administration, and another study examined the effectiveness and tolerability of IPC compared to a diet high in iron.

A total of approximately 700 pregnant women with normal and reduced stored level were included, of which more than 400 patients received IPC.

Treatment with IPC in pregnant women showed similar improvements in haematological parameters compared to results with IPC in non-pregnant patients with good tolerability. In the comparative clinical studies, an improvement in the hemoglobin value after 30 days up to 2.5 months of treatment with IPC compared to the start of treatment was observed on average of 0.72 to 2.2 g/dL ($p < 0.05$). In addition, improvements in the serum ferritin (+5.74 mcg/l) and the ferrite content of the red blood cells (on average +6.3 mcg/g and 5.74 mcg/g after 30 days and 2.5 months of treatment compared to baseline) were measured.

An open study examined the effectiveness of IPC (200 mg IPC/day for 10 days and 100 mg/day for 20 days) with the addition of vitamin B12 in pregnant women with iron deficiency anemia. This showed a significant increase in hemoglobin values, as well as hematocrit, number of erythrocytes and folic acid values ($p < 0.01$).

An open study in 43 young adults with varying degrees of severity of iron deficiency anemia between the ages of 14.5 and 17 years examined the effectiveness of IPC on hemoglobin values. The changes in the Hb value after 48 to 49 days of treatment compared to baseline were 10.44 ± 0.08 g/dL, 11.64 ± 0.07 g/dL and 13.41 ± 0.13 g/dL in mild, moderate or severe anemia, and after 75- up to 76 days of treatment 13.32 ± 0.11 g/dL and 12.64 ± 0.07 g/dL (moderate and severe anemia).

5.2 Pharmacokinetic properties

Absorption

Studies with radiolabeled IPC show a good correlation between iron absorption and the iron incorporation into hemoglobin. The relative amount of absorbed iron correlates with the extent of iron deficiency (i.e. the higher the iron deficiency, the better the iron absorption). In contrast to iron (II) salts, no negative impact of food on the bioavailability of iron from IPC was found: A significantly increased bioavailability of iron with concomitant food intake was demonstrated in one clinical study, while three further studies showed a positive trend but no clinically relevant effects.

Approximately 80% of folic acid is absorbed in the small intestine, with an absorption maximum after 30-60 minutes.

Elimination

Unabsorbed iron is excreted through the faeces. Folic acid is mainly excreted in the urine.

5.3 Preclinical Safety Data:

Nonclinical data established with iron polymaltose revealed no special hazard for humans based on conventional studies of single dose and repeated dose toxicity, genotoxicity and reproductive and developmental toxicity.

The LD50 for IPC, which, as determined in animal studies with mice and rats was greater than an orally administered dose of 2,000 mg iron per kg body weight.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipient(s)

Iron [III] Hydroxide Polymaltose Complex
Folic Acid
Lactose Monohydrate
Sodium Lauryl Sulphate
Magnesium Stearate
EHG Capsule '2' printed 'OROFER' Scar/Scarlets

6.2 Incompatibilities

No incompatibilities

6.3 Shelf-life

24 Months

6.4 Special precautions for storage

Store in a dry place, below 30°C.

6.5 Nature and contents of container

2 Blister strips of 20 capsules each are packed in a printed carton along with a leaflet.

6.6 Instructions for use and handling

Dosage and duration of therapy is dependent upon the extent of iron deficiency. In case of iron deficiency, the therapy takes about 3-5 months until normalization of the hemoglobin value is achieved. Afterwards, the therapy should be continued for several weeks to replenish the iron stores.

7. MARKETING AUTHORISATION HOLDER

Emcure Pharmaceuticals Ltd. Bhosari, Pune

8. MARKETING AUTHORISATION NUMBER(S)

04-2765

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27.09.2007

10. DATE OF REVISION OF THE TEXT

02.06.2021