Medifer 50mg/ml

Pharmaceutical form: Oral drops

Composition: 1 ml (20 drops) contains: active substance: 178.6 mg iron (III) polymaltose hydroxide polymaltose complex, in terms of iron 50 mg.
Excipients: sucrose, sodium methylparahydroxybenzoate, sodium propylparahydroxybenzoate, citric acid monohydrate, caramel flavor, purified water.
Pharmacological group: iron drug.

Pharmacodynamics:
In the iron(III)-hydroxide polymaltose complex, the polynuclear iron (III)-hydroxide core is superficially surrounded by a number of non-covalently bound polymaltose molecules resulting in an overall average molecular weight of approximately 50 kDa. The structure of polynuclear core of iron (III)-hydroxide polymaltose complex has a similar with the core structure of the ferritin protein - the physiological depo of iron. Iron(III)-hydroxide polymaltose complex is a stable complex and does not release large amounts of iron under physiological conditions. Because of its size, the extent of diffusion of iron(III)-hydroxide polymaltose complex through the membrane of the mucosa is about 40 times less than that of the hexaquo iron(II) complex. Iron from iron (III) polymaltose hydroxide complex is actively absorbed in the intestine. The effectiveness of the drug in normalizing the content of hemoglobin (Hb) and replenishing the iron depo has been demonstrated in numerous randomized controlled clinical trials using placebo control or an active comparator conducted in adults and children with various iron depo status.
Pharmacokinetics:
Iron from iron (III) polymaltose hydroxide is absorbed in accordance with a controlled mechanism. The increase in serum iron after the use of the drug does not correlate with the total absorption of iron, measured as incorporation into hemoglobin (Hb). Studies with a labeled radioisotope of iron (III) hydroxide polymaltosate revealed a strong correlation between the inclusion of iron in erythrocytes and the iron content throughout the body. The maximum activity of iron absorption from iron (III) hydroxide polymaltosate occurs in the duodenum and small intestine. As in case of other oral iron drugs, the relative absorption of iron from iron (III) hydroxide polymaltosate defined as incorporation into hemoglobin, decreases with increasing doses of iron. In addition, a correlation was observed between the degree of iron deficiency (in particular serum ferritin concentration) and the relative amount of absorbed iron (i.e., the greater the iron deficiency, the better the relative absorption). In patients with anemia, absorption of iron from iron (III) hydroxide polymaltosate, in contrast to iron salts, increased in the presence of food. Iron absorbed in the gastrointestinal tract is transported to the blood, where it immediately binds to transferrin. Transferrin-bound iron is distributed to sites where it is needed or to storage organs such as the liver and spleen. Distribution of iron from iron (III) hydroxide polymaltosate after absorption was studied in a study using the technique of double isotopes (^{55}Fe and ^{59}Fe). The absorbed iron binds to

transferrin and is used to synthesize hemoglobin (Hb) in the bone marrow or is stored, mainly in the liver, where it binds to ferritin. Most of the iron is incorporated into the oxygen transport protein hemoglobin (Hb) during erythropoiesis in the bone marrow or stored as ferritin. Iron from erythrocytes is recycled at the end of their life cycle. The breakdown products of polymaltose (maltose and gluconate) are converted into glucose, which is used in intermediate metabolism.

Indications:

Treatment of iron deficiency without anemia (latent iron deficiency) and symptomatic iron deficiency anemia.

Contraindications:

- iron overload (e.g., hemosiderosis, hemochromatosis);
- impairment of iron utilization (e.g., lead anemia, sideroachrestic anemia, thalassemia);
- anemia other than iron deficiency anemia (e.g., haemolytic anemia, megaloplastic anemia due to vitamin B12 deficiency);
- sucrase / isomaltase deficiency, fructose intolerance, glucose-galactose malabsorption.

Warnings and precautions:

Warning for diabetics

Medifer is not expected to have an effect on the daily insulin requirement in patients with diabetes mellitus. 1 chewable tablet contains 0,01 bread units.

Anemia can be caused by infectious diseases or malignant neoplasms. Since iron can only be taken after the root cause of the disease has been eliminated, the benefit/risk ratio of treatment should be determined.

During treatment with Medifer, dark discoloration of feces can be noted, but this is not clinically significant.

Medifer should be used with caution in patients undergoing repeated blood transfusion to avoid iron overload. Interactions of iron (III) hydroxide polymaltosate complex with tetracycline or aluminum hydroxide have been studied. No significant decrease in tetracycline absorption has been observed. Plasma concentrations of tetracycline did not drop below the minimal inhibitory level, necessary for bacteriostasis. . Absorption of iron from iron (III) hydroxide polymaltosate did not decrease under the influence of aluminum hydroxide or tetracycline. Thus, concomitant administration of iron (III) hydroxide polymaltosate with tetracycline and other phenolic compounds, as well as aluminum hydroxide, is allowed. The studies in rats using tetracycline, aluminum hydroxide, acetylsalicylic acid, sulfasalazine, calcium carbonate, calcium acetate and calcium phosphate in combination with vitamin D3, bromazepam, magnesium aspartate, D-penicillamine, methyldopa, paracetamol and auranofin revealed no interactions with iron (III) hydroxide polymaltosate.

The administration of the drug does not affect the results of the detection of hidden blood (with a selective determination of hemoglobin), therefore, treatment interruption is not necessary.

Medifer with food, drinks and alcohol

Concomitant use of parenteral and oral iron drugs should be avoided, since the absorption of iron taken orally slows down.

No interaction of iron (III) hydroxide polymaltosate with food components such as phytic acid, oxalic acid, tannin, sodium alginate, choline and choline salts, vitamin A, vitamin D3, and vitamin E, soybean oil and soybean flour was observed either. These results indicate that iron (III) hydroxide polymaltosate can be administered during or immediately after meals.

Administration during pregnancy and breastfeeding

Pregnancy

Until now, there have been no reports of serious adverse reactions after oral administration of Medifer at therapeutic doses for the treatment of anemia during pregnancy. The data obtained from animal studies showed no danger to the fetus or the mother. There is no clinical data on the use of Medifer in the I trimester of pregnancy (the drug is prescribing only in the I and III trimesters).

The studies conducted in pregnant women after the end of the I trimester of pregnancy revealed no adverse effects of Medifer in mothers and/or newborns. Consequently, adverse effect on the fetus is unlikely following the administration of Medifer.

Breastfeeding

Woman breast milk contains iron bound to lactoferrin. The amount of iron that passes from iron (III) hydroxide polymaltosate to breast milk is unknown. It is unlikely that the administration of iron (III) hydroxide polymaltosate in lactating women can lead to adverse effects in the child.

Fertility

As a precaution to women of childbearing age and women during pregnancy and lactation, Medifer should be administered only after consultation with the doctor. The benefit/risk ratio should be evaluated.

Posology and method of administration

Table 1. Daily doses of children and adults according to age.

Category of patients	**Treatment of iron deficiency anemia**	**Treatment of iron deficiency without anemia**
Premature	Data are presented in Table 2	
Children of the first year of life	10-20 drops (25-50 mg of Iron)	6-10 drops (15-25 mg of Iron)
Children from 1 to 12 years	20-40 drops (50-100 mg of Iron)	10-20 drops (25-50 mg of Iron)
Children over aged 12 years	40-120 drops (100-300 mg of Iron)	20-40 drops (50-100 mg of Iron)

Table 2. Daily doses of children and adults according to weight.

Category of patients	Treatment of iron deficiency anemia	Treatment of iron deficiency without anemia
Children (less than 15 kg) and premature newborns	1-2 drops (2,5-5 mg of Iron) per 1 kg of weight	1 drop (2,5 mg of Iron) per 1 kg of weight
Children (15-30 kg)	20-40 drops (50-100 mg of Iron)	10-20 drops (25-50 mg of Iron)
Children (from 30 kg) and adults	40-120 drops (100-300 mg of Iron)	20-40 drops (50-100 mg of Iron)

Treatment of iron deficiency anemia in children and adults

Treatment to achieve normal hemoglobin (Hb) takes for 3–5 months. After this, treatment should be continued for several weeks at the dose described for iron deficiency without anemia in order to replenish iron stores.

Treatment of iron deficiency without anemia

Treatment takes approximately 1 to 2 months.

Method of administration

For oral administration.

The daily dose can be divided into several doses or taken at a time.

Medifer should be administered during or immediately after meals.

Medifer can be mixed with fruit and vegetable juices, baby food or soft drinks. Slight coloring of the mixture does not affect the taste of the juice/baby food, nor the effectiveness of the drug.

To accurately measure the dose of the drug, the vial should be held vertically. Drops should flow out immediately. If this does not happen, lightly tap the vial until a drop appears.

Do not shake the vial.

Side effects

System/organ/class	Very common (≥1/10)	Common (≥1/100, < 1/10)	Not Common (≥1/1000, < 1/100)	Rarly (> 1/10 000, < 1/1000)
Nervous system disorders	--	--	Headache	--
Gastrointestinal disorders	Feces discolouration[1]	diarrhea, nausea, abdominal pain[2], constipation	Vomiting[3], discoloration of tooth enamel, gastritis	--
Skin and subcutaneous tissue disorders	--	--	itching, rash[5,6], urticaria, erythema	--
Musculoskeletal and connective tissue disorders	--	--	--	muscle spasms[4], myalgia

[1] *Fecal discoloration has been reported with less frequency in the meta-analysis, but is a well-studied reaction that occurs with oral iron treatment in general. In this regard, this adverse reaction was assigned a frequency of occurrence of "very common";*

[2] *Includes: abdominal pain, dyspepsia, epigastric discomfort, bloating;*

[3] *Includes: vomiting, belching;*

[4] *Includes: involuntary muscle contractions, tremors;*

[5] *Includes: rash, rash macular, rash vesicular;*

[6] *Adverse reactions that were noted in the post-marketing period with an estimated incidence of <1/491 patients (upper limit of 95 % confidence interval).*

Storage conditions:

3 years.

Open containers should be used within 6 months.

Store in original package at temperature below 25 °C.

Packaging:

30 ml amber Glass Bottles with PE Cap/dropper and Patient Information Leaflet completed in a Paperboard box.

Regulatory status:

Prescription only.