Maltofer®

Drops

Pharmaceutical form: oral solution

Qualitative and quantitative composition1 ml (20 drops) contains 50 mg of iron as iron(III)-hydroxide polymaltose complex (IPC).

Excipients: purified water, sucrose, cream essence, sodium methyl hydroxybenzoate (E219), sodium propyl hydroxybenzoate (E217) and sodium hydroxide.

Properties/Effects

Pharmacotherapeutical group: iron preparation.

ATC Code: B03AB05

Maltofer® drops are an iron preparation for the treatment of iron deficiency without anaemia and iron deficiency anaemia.

Iron is an important constituent of haemoglobin, myoglobin, and iron-containing enzymes. In general, iron deficiency can cause chronic fatigue, lack of concentration and reduced mental performance, irritability, anxiety, headache, loss of appetite, susceptibility to infection, conspicuous paleness, cracks at the corners of the mouth (rhagades), dry skin and brittle hair and nails.

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 polynuclear core of IPC has a structure similar to that of the physiological iron storage protein, ferritin. IPC is a stable complex and does not release large amounts of iron under physiological conditions. Because of its size, the extent of diffusion of IPC through the membrane of the mucosa is about 40 times less than that of the hexaquo-iron(II) complex. Iron from IPC is taken up in the gut via an active mechanism. In contrast to iron(II) salts, IPC does not have pro-oxidative properties.

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

Pharmacokinetics

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 Maltofer: 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.

Preclinical 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.

Therapeutic indications

Treatment of iron deficiency without anaemia and iron deficiency anaemia.

Prophylactic therapy of iron deficiency to cover the recommended daily dietary allowances (RDA) during pregnancy and lactation, for children, adolescents and adults (e.g. vegetarians and elderly).

Posology

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

Iron deficiency anaemia: the therapy takes about 3–5 months until a normalisation of the haemoglobin value is achieved. Afterwards the therapy should be continued for several weeks, or for pregnant women, at least until the end of the pregnancy with a dosage such as described for iron deficiency without anaemia in order to replenish the iron stores.

Iron deficiency without anaemia: the therapy takes about 1–2 months.

Table 1 Dosage of Maltofer® Oral Drops According to Age

Patient	Iron deficiency anaemia	Iron deficiency without anaemia	Prophylactic therapy
Premature births	Refer to table 2	Refer to table 2	Refer to table 2
Infants (up to 1 year)	10–20 drops daily (25–50 mg iron)	6–10 drops daily (15–25 mg iron)	2–4 drops daily (5–10 mg iron)
Children (1–12 years)	20–40 drops daily (50–100 mg iron)	10–20 drops daily (25–50 mg iron)	4–6 drops daily (10–15 mg iron)
Children (>12 years), adults	40–120 drops daily (100–300 mg iron)	20–40 drops daily (50–100 mg iron)	4–6 drops daily (10–15 mg iron)
Pregnant women	80–120 drops daily (200–300 mg iron)	40 drops daily (100 mg iron)	20–40 drops daily (50–100 mg iron)

Table 2 Dosage of Maltofer® Oral Drops According to Body Weight

Patient	Treatment of iron deficiency anaemia	Treatment and prevention of iron deficiency without anaemia
Infants (<15 kg) and premature births	2.5-5 mg iron per kg body weight daily (1-2 drops per kg body weight daily)	2.5 mg iron per kg body weight daily (1 drop per kg body weight daily)
Children (15-30 kg)	50-100 mg iron daily (20-40 drops daily)	25-50 mg iron daily (10-20 drops daily)
Children (>30 kg) and adults	100-300 mg iron daily (40-120 drops daily)	50-100 mg iron daily (20-40 drops daily)

Method of administration

The daily dosage can be divided into separate doses or can be taken all at once. Maltofer® drops should be taken during or immediately after a meal. Maltofer® drops can be mixed with fruit and vegetable juices or with bottle-feed. The slight discolouration of the mixture does not affect either the efficacy of the product or the taste of the drink to which it is added. To ensure accurate dosing of

Maltofer® drops, the bottle needs to be held upside down and vertical. The drops should flow immediately. If this does not happen, tap the bottle gently until a drop forms. Do not shake the bottle.

Contraindications

- Known hypersensitivity or intolerance to iron(III)-hydroxide polymaltose complex or any of the excipients
- Iron overload (e.g. haemochromatosis, haemosiderosis)
- Disturbances in iron utilisation (e.g. anaemia from lead-poisoning, sidero-achrestic anaemia, thalassaemia)
- Anaemia not caused by iron deficiency (e.g. haemolytic anaemia or megaloblastic anaemia due to vitamin B12 deficiency).

Special warnings and special precautions for use

1 mL of Maltofer droplets contains 6 mg of sodium. This corresponds to 0.3% of the WHO-recommended maximum daily intake of 2 g of sodium for adults.

Maltofer droplets contain sodium methyl hydroxybenzoate (E219) and sodium propyl hydroxybenzoate (E217). These can cause allergic reactions, even delayed reactions.

Information for diabetics: Maltofer® drops contain 50 mg of sucrose per 1 ml of drops (=20 drops), equivalent to 0.01 bread units per ml (20 drops).
Patients with a rare hereditary fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase deficiency should not use this medicinal product. Sucrose can be harmful to the teeth.

Infections or tumours may cause anaemia. Since iron can be utilised only after correcting the primary disease, a benefit/risk evaluation is advisable.

During treatment with Maltofer®, there may be dark discolouration of the faeces (stools).

Interactions with other medicinal products and other forms of interaction

Interactions of IPC with tetracycline or aluminium hydroxide were investigated in 3 human studies (crossover design, 22 patients per study). 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 bacteriostatic serum levels. Iron absorption from IPC was not reduced by aluminium hydroxide or tetracycline.

Iron(III) hydroxide polymaltose complex can therefore be administered at thesame time as tetracycline or other phenolic compounds, as well as aluminium hydroxide.

Studies in rats with tetracycline, aluminium hydroxide, acetylsalicylate, sulphasalazine, calcium carbonate, calcium acetate and calcium phosphate in combination with vitamin D3, bromazepam, magnesium aspartate, Dpenicillamine, methyldopa, paracetamol and auranofin have not shown any interactions with IPC.
Similarly, no interactions 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 with IPC.

These results suggest that IPC can be taken during or immediately after food intake.

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

Concomitant administration of parenteral and oral iron is not recommended since the absorption of oral iron would be inhibited.

Pregnancy and lactation

Pregnancy
Clinical data of exposed pregnancies exhibited no undesirable effects on pregnancy or on the health of the foetus or newborn infant. Data from epidemiological studies is not available. Animal studies did not show any reproductive toxicity. Caution is advised for use during pregnancy. As a precautionary measure, Maltofer should only be taken after consulting a doctor.

Breast-feeding
It is not known whether iron from the iron(III)-hydroxide polymaltose complex is excreted in human milk. Human milk naturally contains iron bound to lactoferrin. As a precautionary measure, Maltofer should only be taken during breast-feeding after consulting a doctor.

Undesirable effects

The safety and tolerability of Maltofer© has been evaluated in a Meta-analyisis of 24 publications or clinical study reports encompassing a total number of 1473 exposed patients.

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 gastrointestional disorders (Nausea, Constipation, Diarrhoea and abdominal pain).

Table 3 Adverse Drug Reactions Detected in Clinical Trials and Post Marketing Setting

System Organ Class	Very common (≥1/10)	Common (≥1/100, <1/10)	Uncommon (≥1/1,000, <1/100)	Rare (<1/1,000)
Gastrointestinal Disorders	Discoloured Faeces*	Diarrhoea, nausea, constipation, abdominal pain (including: abdominal pain, dyspepsia, epigastric discomfort, abdominal distension)	Vomiting (including: vomiting, regurgitation), Tooth discolouration, gastritis	
Skin and Subcutaneous Tissue Disorders			Rash (including: rash, macular rash, bullous rash)**, urticaria**, erythema**., pruritus	
Nervous System Disorders			Headache	
Musculoskeletal and connective tissue disorders				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).

Overdose

There are no reported cases of overdose leading to acute iron toxicity nor iron overload.

Storage

Keep all medicines out of reach of children.

Do not store above 30 °C.

Keep the glass bottle in the original package (i.e. outer carton) in order to protect from light.

Presentation

30 ml Type III brown glass bottle with inserted dropper applicator and closed with a tamper-evident screw cap. On prescription only.

Manufactured by Vifor SA (Switzerland) for Vifor (International) Inc.(Switzerland)

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