Product	Maltofer 150 Syrup	
Country	Malaysia	
Manufacturer	COV	
SAP Number	3005249-04S	**Min. Ver.:** 03
Manufacturer Identification Number	XXXXXXX/XX	
Fonts	Helvetica (min. 9 pt)	
Dimensions	180 x 320 mm	

Colours/Flats
Black

Non-Printed Colours
Dye Cut

ID: 2304-044

XXX
Read Direction

Maltofer®

Syrup

Pharmaceutical form: oral solution, cream flavour

Qualitative and quantitative composition
1 ml contains 10 mg of iron as iron (III)-hydroxide polymaltose complex (IPC)

Excipients: purified water, sorbitol solution (70%), sucrose, ethanol (96%), cream essence, methyl hydroxybenzoate (E218), propyl hydroxybenzoate (E216) and sodium hydroxide.

Properties
Pharmacotherapeutical group: iron preparation.

ATC Code: B03AB05

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.

Therapeutic Indications
Treatment of iron deficiency without anaemia and iron deficiency anaemia. Prophylactic therapy of iron deficiency during pregnancy.

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 to replenish the iron stores.

Table 1. Dosage in children and adults according to age

	Iron deficiency anaemia	Iron deficiency without anaemia	Prophylactic therapy
Infants (up to 1 year)	2.5–5 ml daily (25–50 mg iron)	–*	–*
Children (1–12 years)	5–10 ml daily (50–100 mg iron)	2.5–5 ml daily (25–50 mg iron)	–*
Children (>12 years), adults	10–30 ml daily (100–300 mg iron)	5–10 ml daily (50–100 mg iron)	–*
Pregnant women	20–30 ml daily (200–300 mg iron)	10 ml daily (100 mg iron)	5–10 ml daily (50–100 mg iron)

*Due to the lower required doses, these indications can only be treated with iron in drop form, such as Maltofer® drops.

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

Method of Administration
The daily dosage can be divided into separate doses or can be taken all at once. Maltofer® syrup should be taken during or immediately after a meal. Maltofer® syrup 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. The supplied measuring cup is used for an exact administration of the dosage.

Pharmacodynamic
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=0.93]. Increases 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.

Pharmacokinetic
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.

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

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. lead anaemia, sideroachrestic 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
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.

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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); however this is of no clinical relevance.

1 mL of Maltofer 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 Maltofer 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 Maltofer syrup contains 200 mg of sucrose. Diabetes patients must take this into account. Sucrose can be harmful to the teeth.

Maltofer syrup contains small quantities of ethanol (alcohol) of less than 100 mg per 30 mL (maximum daily dose).

Maltofer syrup contains methyl hydroxybenzoate (E218) and propyl hydroxybenzoate (E216). These can cause allergic reactions, even delayed reactions.

Interactions with other medicaments 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 level necessary for efficacy. Iron absorption from IPC was not reduced by aluminium hydroxide or tetracycline Iron(III) hydroxide polymaltose complex can therefore be administered at the same 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, D-penicillamine, 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 or oral iron would be inhibited and parenteral iron preparations may only be used if oral treatment is not suitable.

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 (see Preclinical Data). 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.

Effects on ability to drive and use machines

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

Undesirable effects

The safety and tolerability of Maltofer® 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).

Discoloured faeces 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).

Table 2. Adverse drug reactions (ADRs) 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, abdominal pain (including: abdominal pain, dyspepsia, epigastric discomfort, abdominal distension), constipation	Vomiting (including: vomiting, regurgitation), teeth discolouration, gastritis	
Skin and Subcutaneous Tissue Disorders			Pruritus, rash (including: rash, macular rash, bullous rash)**, urticaria**, erythema**	
Nervous System			Headache	
Musculoskeletal and connective tissue disorders				Muscle spasms (including: involuntary muscle contraction, tremor), myalgia.

* Discoloured faeces 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

In cases of overdose, iron accumulation or intoxication is unlikely with Maltofer® due to the low toxicity of iron(III)-hydroxide polymaltose complex (i.e., in mice or rats: lethal dose, 50% (LD50) >2,000 mg Fe/kg body weight) and controlled uptake of iron. No cases of accidental poisoning with fatal outcome have been reported.

Storage

Below 30 °C in the original container. Discard 2 months after opening. Keep all medicines out of reach of children. Keep in the original package (i. e. outer carton) in order to protect from light.

Presentation

150 ml Type III brown glass bottle, closed with tamper-evident screw cap. A measuring cup for administration covers the screw cap.

Manufactured by Corden Pharma Fribourg SA (Switzerland) for Vifor (International) Inc. (Switzerland)

Product Registration Holder

Zuellig Pharma Sdn Bhd No.15 Persiaran Pasak Bumi,
Seksyen U8, Perindustrian Bukit Jelutong, 40150 Shah Alam,
Selangor Darul Ehsan, Malaysia

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