

MALTOFER

PRODUCT INFORMATION

MALTOFER TABLETS
MALTOFER SYRUP
MALTOFER DROPS

NAME OF THE MEDICINE

Iron polymaltose (AAN)

Chemical structure

Iron polymaltose (IPC), the active substance of MALTOFER, is a macromolecular complex in which polynuclear iron(III)-hydroxide is stabilized by polymaltose. It contains about 53% (m/m)* iron(III)-hydroxide, equivalent to about 27% (m/m) of iron, about 36% (m/m) polymaltose ligand, less than 6.4% (m/m) sodium chloride and less than 10% (m/m) of water. It is stable and highly water-soluble over a broad pH range, and, unlike simple iron(III)-oxide or iron(III)-hydroxide, does not precipitate even in an alkaline environment.

CAS-Number 53858-86-9

DESCRIPTION

MALTOFER TABLETS are film-coated, reddish brown, round and biconvex tablets. The tablet contains 100 mg iron as iron polymaltose as the active ingredient. The tablets also contain crospovidone, hydroxypropylcellulose, hypromellose, iron oxide red, iron oxide yellow, macrogol 6000, magnesium stearate, cellulose - microcrystalline and titanium dioxide.

MALTOFER SYRUP, oral liquid is a dark brown solution which contains 50 mg/5 mL iron as iron polymaltose as the active ingredient. The oral solution also contains cream flavour, ethanol, methyl hydroxybenzoate, propyl hydroxybenzoate, water - purified, sodium hydroxide, sorbitol solution (70%) (non-crystallising), and sucrose.

MALTOFER DROPS, oral liquid is a dark brown solution which contains 50 mg/mL iron as iron polymaltose as the active ingredient. The oral liquid also contains water - purified, sucrose, cream flavour, sodium methyl hydroxybenzoate, sodium propyl hydroxybenzoate and sodium hydroxide.

*Mass fraction mass/mass

MALTOFER

PHARMACOLOGY

In MALTOFER, 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 which is so large that the extent of diffusion through the membrane of the mucosa is about 40 times less than that of the hexaquo-iron(II) complex. Iron polymaltose is stable and does not release large amounts of iron under physiological conditions. The polynuclear core of iron polymaltose is hypothesized to have a structure similar to that of the core of the physiological iron storage protein, ferritin.

Pharmacokinetic properties

The information on MALTOFER was drawn from different formulations and dosage forms including chewable tablets and oral liquids. In vitro studies have shown that MALTOFER chewable tablets and MALTOFER film-coated tablets have comparable dissolution rates.

Absorption, Distribution, Metabolism, Excretion

The iron absorbed from iron polymaltose (referred to MALTOFER) is used in the bone marrow for haemoglobin (Hb) synthesis or is stored, mainly in the liver, bound to ferritin. Iron that is not absorbed is excreted via the faeces.

The iron of MALTOFER is absorbed by a controlled mechanism. Studies with radiolabelled iron polymaltose showed that there is a good correlation between the percentage of erythrocyte uptake (incorporation in Hb) and the absorption quantified by whole body count^{1,2}. The highest absorption of iron from iron polymaltose is in the duodenum and ileum³. As with other oral iron preparations, the relative absorption of iron from MALTOFER, measured as incorporation in Hb, decreased with increasing doses of iron. A correlation between the extent of iron deficiency and the relative amount of iron absorbed was also observed (i.e., the higher the iron deficiency, the better the relative absorption). Absorption of iron from MALTOFER is markedly reduced in humans. Iron uptake of MALTOFER has been assessed with different IPC formulations. The information reported below is directly related to MALTOFER products. The fasting and fed plasma iron concentration-time curves showed markedly reduced absorption of iron from MALTOFER liquid compared with ferrous sulfate/ascorbic acid liquid over the first 8 hours following single oral doses in healthy young men with experimentally induced iron deficiency anaemia⁴. In the fasting state, only $1.2 \pm 1.0\%$ (mean \pm SD) of the iron from MALTOFER liquid was absorbed compared with $43.7\% \pm 7.1\%$ of the iron from ferrous sulfate/ascorbic acid liquid formulation ($p < 0.001$). In the fed state, $8.8 \pm 4.7\%$ of the iron from MALTOFER liquid was absorbed compared with $43.0 \pm 5.0\%$ of the iron from ferrous sulfate/ascorbic acid liquid formulation ($p < 0.001$). The results suggest that greater absorption of iron over the first 8 hours following administration occurs when MALTOFER liquid is administered with food compared with the fasting state. Administering MALTOFER with food in iron deficient subjects increases iron uptake into erythrocytes.

Similar results were noted after 28 days of oral treatment with iron utilization (Hb levels and serum ferritin concentrations) being higher in the FS group (17%) compared to MALTOFER (12%).

CLINICAL TRIALS

The efficacy of MALTOFER in normalising Hb and replenishing iron store levels has been demonstrated in several randomised, placebo or reference-therapy controlled clinical trials conducted in adults and adolescents (greater than 12 years of age) with varying iron status.

Adults and Adolescents

Eleven controlled clinical studies have been performed with MALTOFER in adult subjects, including 9 trials where MALTOFER was compared to treatment with ferrous preparations, 2 placebo-controlled trials, and one trial comparing MALTOFER to no treatment⁶⁻¹². These trials included a total of approximately 900 subjects, with approximately 500 receiving MALTOFER. The clinical data available for iron deficiency anaemia are up to 3 months of treatment, and up to 6 months of treatment for iron deficiency without anaemia.

No efficacy data is available related to Hb or serum ferritin concentrations after 6 months of MALTOFER treatment in non-anaemic patients with iron deficiency.

Placebo-controlled Clinical Trials in Adults

There were 2 placebo controlled trials that included a total of 91 subjects, of whom 37 received MALTOFER chewable tablets.

In a randomised, placebo-controlled, single-blind study, Macintosh and Jacobs⁸ compared 56 days of treatment with MALTOFER chewable tablets containing 100 mg iron twice daily versus placebo. The subjects were healthy males who had donated blood in the preceding 12 months. At the start of the study, subjects had normal Hb (≥ 135 g/L) and either normal (serum ferritin 50-150 ng/mL) or deficient (serum ferritin < 20 ng/mL) iron stores. Treatments were administered with food. A significant rise in Hb (from 143 to 150 g/L; $p=0.03$) and repletion of body iron stores (rise in serum ferritin from 16.2 to 43.2 ng/mL; $p=0.002$) was seen in iron deficient (ID) subjects ($n=11$) treated with MALTOFER. In ID subjects receiving placebo ($n=12$), there was no statistically significant Hb change (143 to 149 g/L; $p=0.064$), although a small but statistically significant rise in serum ferritin (16.7 to 27.3 ng/mL; $p=0.02$) was observed. Neither placebo nor MALTOFER produced a statistically significant change in Hb or serum ferritin in the non-ID control subjects. This study confirms that MALTOFER will replenish iron stores in ID subjects, but not in non-ID subjects.

The second clinical trial primarily tested the hypothesis that the availability of iron influences lipid peroxidation⁹. All male subjects ($n=45$) with iron deficiency (serum ferritin ≤ 30 μ g/L and some exhibited hypochromic microcytic anaemia) were randomized into three parallel groups and treated with either, MALTOFER, ferrous sulfate (FS), or placebo for 6 months, twice daily with meals. Subjects received 200 mg of iron/day as MALTOFER chewable tablets, or 180 mg/day of iron as micro-capsulated FS, or placebo. A 50 mg ascorbic acid tablet was taken together with the FS or placebo supplements. Three subjects in the FS group, and 2 in the MALTOFER group reported stomach problems. In both groups, 1 subject discontinued treatment because of stomach problems, while for the three remaining, the dose was halved. When compared with the placebo, both FS and MALTOFER treatments increased Hb, serum and erythrocyte ferritin levels. Hb increased in the MALTOFER group (3.3 ± 2.2 g/L) and the FS group (1.5 ± 1.5 g/L) (Table 1). The increase in serum ferritin (a routine clinical diagnostic marker for anaemia) from baseline was significantly greater in the FS group (2.2-fold) than the MALTOFER group (1.3-fold), whereas erythrocytic ferritin (diagnostic marker not routinely used in the clinical setting) increased similarly in both active treatment groups (+36% FS; +27% MALTOFER) (Table 1).

MALTOFER

Table 1: Iron status (mean values) at baseline and following 6 months treatment; placebo vs MALTOFER and ferrous sulfate (FS) vs placebo⁹.

| Treatment | n | Haemoglobin g/L; change (SEM) | | | Serum ferritin µg/L; change (SEM) | | | Erythrocyte ferritin µg/cell; change (SEM) | | |
|-----------|----|-------------------------------|------------|----------------------|-----------------------------------|------------|---------------------|--|------------|---------------------|
| | | Before | Change | P value ¹ | Before | Change | P value | Before | Change | P value |
| Placebo | 15 | 144.1 | -3.6 (1.2) | < 0.05 ¹ | 19.5 | 5.0 (3.4) | < 0.05 ¹ | 17.7 | -2.9 (1.7) | < 0.05 ¹ |
| MALTOFER | 15 | 144.9 | 3.3 (2.2) | | 20.5 | 27.4 (4.3) | | 16.9 | 4.6 (2.4) | |
| FS | 15 | 145.3 | 1.5 (1.5) | NS ² | 21.5 | 46.8 (8.5) | < 0.05 ² | 15.9 | 5.8 (2.2) | NS ² |

¹ P value: IPC vs Placebo; ² P value: IPC vs FS; Note – the three groups were compared using one-way ANOVA, between group comparisons with Duncan Multiple Range Tests, and 95% CI were calculated based on the t-distribution.

Reference-controlled Studies

In reference drug controlled studies, the efficacy of MALTOFER compared to FS in adults with iron deficiency anaemia (IDA) indicate that FS is more efficient than MALTOFER for this indication based on more efficient replenishment of depleted total body iron stores and shorter times to achieve normalization of Hb levels. Mean Hb levels at weeks 9 and 12 are similar for both treatment arms. However, there are limited comparative data on the proportion of subjects achieving normalization of Hb levels. No longer term efficacy data was available for MALTOFER in patients with IDA.

Short-term Reference-controlled Studies (<12 Weeks Duration)

In a double-blind study, the efficacy and tolerability of MALTOFER was compared with FS for the treatment of iron deficiency anaemia (IDA) in adults¹⁰. 121 adults with IDA (defined as Hb 8.5-12.0 g/dL, MCH < 28 pg and/or MCHC < 33 g/dL) were randomised to receive either MALTOFER chewable tablets (100 mg iron twice daily [200 mg iron/day] with meals) or FS (60 mg iron three times daily [180 mg iron/day] 30 minutes before meals) for 9 weeks. The intention-to-treat analysis (ITT) included 104 patients (52 patients in each group: 7 male, 45 female). In total, 89 patients completed the 9 week study, and 17 in the MALTOFER group and 15 in the FS group discontinued before the end of the study. In total, 47 patients completed the study per-protocol (PP). At week 9, Hb results for the two study arms for all patients in the “all patients efficacy analysis” (ie. ITT analysis) and “patients in the PP analysis with at least 9 weeks treatment” are summarized in Table 2. At 9 weeks visit, the Hb levels were below the limit of normal range for 50% (20/40) treated with MALTOFER compared with 29.5% (13/44) of patients treated with FS.

Table 2: Hb (g/dL) levels in “all patients” and per-protocol analyses; mean ± SD¹⁰.

| Treatment | (n) Baseline | (n) Week 3 | (n) Week 6 | (n) Week 9 |
|---|-------------------------------|--------------------------------|---------------------------------|-------------------------------|
| All patients efficacy analysis | | | | |
| MALTOFER 200mg iron/day | (52) 10.89 ± 1.08 | (49) 11.32 ± 1.34 | (42) 11.57 ± 1.18 | (40) 12.11 ± 1.24 |
| FS (180 mg iron/day) | (52) 10.76 ± 0.97 p = 0.49 | (49) 11.83 ± 0.96 p = 0.03* | (44) 12.34 ± 1.31 p = 0.005* | (44) 12.54 ± 1.31 p = 0.13 |
| Patients in the per-protocol analysis with at least 9 weeks treatment | | | | |
| MALTOFER 200 mg iron/day | (22) 10.74 ± 0.88 | (22) 11.34 ± 1.11 | (21) 11.63 ± 1.10 | (22) 12.03 ± 1.51 |
| FS (180 mg iron/day) | (22) 10.93 ± 0.90 p = 0.48 | (23) 11.76 ± 1.07 p = 0.20 | (22) 12.21 ± 1.30 p = 0.12 | (25) 12.39 ± 1.11 p = 0.35 |

* At weeks 3 and 6 in the all patients efficacy analysis, Hb levels are significantly higher in the FS group compared with the MALTOFER group.

Reference-controlled Studies of ≥ 12 Weeks Duration

In a single centre, open-label, randomised, parallel-group study, the efficacy and tolerability of oral MALTOFER drops in comparison to ferrous sulfate syrup in the treatment of IDA was investigated¹¹. Eligible patients had normal laboratory results except for the IDA defined as (Hb <136/120 g/L for men/women; serum ferritin < 20 µg/L). Subjects were assigned to one of the four treatment groups in which all received 100 mg of iron twice daily for 12 weeks: Group 1 received MALTOFER DROPS; Group 2 received MALTOFER DROPS with 0.9 mol/L glycerophosphate; Group 3 received MALTOFER DROPS with 1.8 mol/L glycerophosphate; and Group 4 received an equivalent amount of iron as ferrous sulfate syrup. The ITT analysis included 143 subjects and 91 in the PP analysis. The endpoints were rate of Hb rise and increase in body iron stores reflected in serum ferritin concentration, as well as transferrin saturation. Secondary observations were changes in the proportion of hypochromic red cells during the course of treatment, erythropoietin levels and tolerability of the two formulations. Response in Hb (Table 3), MCV, MCH and red cell count increased to a similar extent in both treatment groups (differences not significant) (per protocol set). Higher serum ferritin was observed in the ferrous sulfate group than the three MALTOFER groups. The most common adverse effect was gastrointestinal tract intolerance occurring significantly more frequently with FS than MALTOFER (44.7% FS group compared to 8.6-17.5% with the MALTOFER groups; p>0.00002).

Table 3: Changes in iron status from baseline to week 12 in the four treatment groups¹¹ (mean ± SD).

| Treatment group | n | Haemoglobin g/L | | Serum ferritin µg/L | |
|---|----|-----------------|------------|---------------------|-------------|
| | | Week 0 | Week 12 | Week 0 | Week 12 |
| Group 1 MALTOFER | 24 | 10.8 ± 0.8 | 12.1 ± 1.1 | 2.9 ± 2.6 | 5.5 ± 4.9 |
| Group 2 MALTOFER +0.9mol/L glycerophosphate | 23 | 10.9 ± 0.8 | 12.3 ± 1.2 | 3.2 ± 2.2 | 5.9 ± 6.6 |
| Group 3 MALTOFER +1.8mol/L glycerophosphate | 24 | 10.8 ± 1.0 | 11.7 ± 1.2 | 3.8 ± 5.0 | 4.8 ± 3.8 |
| Group 4 Ferrous sulfate | 20 | 10.7 ± 0.9 | 12.3 ± 1.5 | 3.5 ± 4.4 | 12.1 ± 11.3 |

Jacobs et al¹², conducted a 12-week, randomised study with using MALTOFER or FS treatment. Blood donors with overt IDA (n=159) were randomly assigned to receive FS containing 60 mg iron twice daily (120 mg/day) in the fasting state (Group 1); 100 mg/day of iron as MALTOFER chewable tablets with breakfast (Group 2); or 200 mg/day of iron as MALTOFER chewable tablets with both breakfast and supper (Group 3). Patients were eligible if their Hb was below normal (< 116/133 g/L, F/M), percentage saturation of transferrin < 17%, or serum ferritin levels < 20 ng/mL. The results for Hb and ferritin are summarized on Table 4.

Table 4: Results of Hb response over 12 weeks of treatment¹² (mean ± SD).

| Treatment group | n | Hb g/L | | | Transferrin saturation % | | | Ferritin µg/L | | |
|--------------------------------------|----|---------------|------------|-----------|--------------------------|-------------|-----------|---------------|-------------|-----------|
| | | Pre-treatment | Wk 12 | RR | Pre-treatment | Wk 12 | RR | Pre-treatment | Wk 12 | RR |
| Group 1 FS: 120 mg iron/day | 45 | 114 ± 8.4 | 132 ± 13.5 | n = 25/32 | 16.8 ± 10.1 | 31.0 ± 11.3 | n = 13/17 | 18.5 ± 27.4 | 36.3 ± 28.8 | n = 16/24 |
| Group 2 MALTOFER: 100 mg iron/day | 40 | 116 ± 9.5 | 126 ± 15 | n = 10/28 | 20.7 ± 17.3 | 22.0 ± 14.0 | n = 4/20 | 13.5 ± 11.9 | 16.5 ± 15.2 | n = 3/34 |
| Group 3 MALTOFER: 200 mg iron/day | 45 | 114 ± 10.5 | 131 ± 9.9 | n = 26/33 | 16.9 ± 10.6 | 27.1 ± 11.9 | n = 14/22 | 14.8 ± 15.7 | 22.0 ± 18.4 | n = 11/38 |

^Response rate (RR) - Individuals who meet the inclusion criteria for study on the basis of low Hb, but having one or other of the iron measurements in the normal range at presentation, are excluded from these tables. For transferrin, exclusions on the basis of a normal ferritin were 16 in each group. At 12 weeks, the number of subjects whose transferrin saturation levels returned to normal was significantly lower for Group 2 than either Group 1 or 3 (P < 0.01). In the ferritin group, exclusions because of normal percentage saturation of transferrin were 11 in Group 1, 4 in Group 2, and 10 in Group 3. At 12 weeks, the number of subjects who ferritin levels returned to normal were significantly better for Group 1 (P < 0.01), while there was no significant difference in Groups 2 and 3.

A similar rise in Hb was noted in with 200 mg/day MALTOFER and 120 mg/day FS. At 12 weeks, all treatments groups showed improvements in Hb levels compared to baseline levels. Increased serum ferritin levels and higher percentage transferrin saturation were reported in the FS group compared to MALTOFER groups.

Studies in adolescents (aged 15 – 18 years)

More than 130 adolescents have been treated with MALTOFER in clinical trials. The efficacy results seen in adolescents were comparable to the results seen in adults¹³⁻¹⁴.

In a placebo-controlled study of 120 adolescents, aged 15 to 18 years, MALTOFER was shown to improve the iron status of adolescents with iron deficiency (with and without anaemia)¹³. Subjects were divided into 4 groups with 30 subjects/group: placebo, control supplement, iron deficient (TSAT* <16%; Hb ≥105/115 g/L F/M), iron deficiency with anaemia (TSAT <16%; Hb <105/115 g/L F/M). The 3 active treatment groups received MALTOFER 100 mg iron/day, 6 days/week, for 8 months. At end of the study, all 3 treatment groups demonstrated significant increases in iron parameters compared to the placebo group, including correction of iron deficiency, anaemia and improvement in iron stores (Table 5). The greatest increase in Hb (+33 g/L) was seen in the IDA group. No gastrointestinal adverse effects were reported.

MALTOFER

Table 5: Effects of MALTOFER treatment in adolescents compared to placebo after 8 months of treatment¹³ (mean ± Standard Error).

| Efficacy Variable | Time Point | MALTOFER | | | Placebo |
|------------------------|--------------|------------|------------|-------------|------------|
| | | IDA | ID | No IDA/ID | No IDA/ID |
| Hb (g/L) | Baseline | 100 ± 2 | 125 ± 2 | 135 ± 2 | 136 ± 2 |
| | End of study | 132 ± 3 | 141 ± 3 | 153 ± 3 | 140 ± 3 |
| | Change | +32.9* | +16.5* | +18.2* | +4.5 |
| Serum ferritin (ng/mL) | Baseline | 10.9 ± 5.5 | 17.8 ± 5.4 | 46.2 ± 5.2 | 62.0 ± 5.2 |
| | End of study | 44.1 ± 8.7 | 43.2 ± 8.5 | 135.6 ± 8.2 | 78.6 ± 8.2 |
| | Change | +33.22* | +25.39* | +89.40* | +16.53 |

*Significant compared to baseline (p<0.01).

Notes: Hb = Haemoglobin; ID = Iron deficiency; IDA = Iron deficiency anaemia;

* TSAT: Transferrin Saturation

Pregnant and breastfeeding women

Clinical studies in pregnant women using MALTOFER alone or MALTOFER in a fixed combination with folic acid (350-400 µg folic acid per tablet) were inconclusive¹⁵⁻²³.

INDICATIONS

Treatment of iron deficiency in adults and adolescents where the use of ferrous iron supplements is not tolerated, or otherwise inappropriate.

Prevention of iron deficiency in adults and adolescents at high risk where the use of ferrous iron supplements is not tolerated, or otherwise inappropriate.

CONTRAINDICATIONS

The use of MALTOFER is contraindicated in the following cases:

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

PRECAUTIONS

Iron deficiency anaemia: All other causes of anaemia should be considered and treated prior to initiating therapy with MALTOFER.

Regular monitoring of the haematologic response is required during MALTOFER therapy as a risk of iron overload and liver damage exists if too much MALTOFER is ingested by haemochromatosis patients over a long period of time. Do not administer to patients with iron overload or haemochromatosis.

The following medicines can affect the absorption of MALTOFER:

- Injectable iron medicines. If the patient is treated with injectable iron medicines, MALTOFER should not be taken in addition to that therapy.

Infections or tumour may cause anaemia. Since iron can be utilised only after correcting

MALTOFER

the primary disease, a benefit/risk evaluation is advisable.

During the treatment with MALTOFER there may be dark discolouration of the faeces (stool), however this is of no clinical relevance.

MALTOFER SYRUP, oral liquid contains the excipients methyl hydroxybenzoate and propyl hydroxybenzoate which may cause allergic reactions (possibly delayed).

MALTOFER SYRUP, oral liquid contains sorbitol and sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

MALTOFER SYRUP, oral liquid contains small amounts of ethanol, 3.25 mg/ml.

MALTOFER DROPS, oral liquid contains the excipients sodium methyl hydroxybenzoate and sodium propyl hydroxybenzoate which may cause allergic reactions (possibly delayed).

MALTOFER DROPS, oral liquid contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Laboratory tests

Regular monitoring of Hb levels and serum ferritin levels should be performed to assess the response to supplementation with MALTOFER as deemed appropriate by the medical practitioner.

Effects on fertility

Fertility studies of iron polymaltose in animals did not reveal any effects on fertility or early embryonic development²⁴.

Use in pregnancy (Category B1)

Australian categorization definition of Category B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage.

Use in lactation

Human breast milk naturally contains iron, which is bound to lactoferrin. The amount of iron passing from iron polymaltose to the mother's milk is unknown.

No effects of iron polymaltose on development or growth of offspring were observed in a pre/post-natal toxicity study in rats, in which nursing dams were treated throughout the pre-weaning lactation period²⁵. Preliminary data from studies conducted in juvenile rats showed no treatment-related adverse effect when immature rats were directly treated orally with iron polymaltose from shortly after birth up to sexual maturity²⁶.

As a precautionary measure, during pregnancy and lactation, MALTOFER should only be used after consulting a medical practitioner. A benefit/risk evaluation is advisable.

MALTOFER

Paediatric use

MALTOFER has not been clearly shown to be effective in children < 12 years of age. The use of MALTOFER in children < 12 years of age is not recommended.

MALTOFER SYRUP contains ethanol.

Use in elderly

Clinical experience with MALTOFER in the elderly is limited. For use in elderly patients consult a medical practitioner.

Carcinogenicity

No long-term studies of tumourigenic potential are available.

Genotoxicity

MALTOFER was not genotoxic in a conventional battery of *in vitro* and *in vivo* tests²⁷⁻²⁹.

INTERACTION WITH OTHER MEDICINES

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

Interactions of MALTOFER with tetracycline or aluminium hydroxide were investigated in human studies (crossover design, 22 patients per study)^{1,2,30-32}. 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 MALTOFER was not reduced by aluminium hydroxide or tetracycline. MALTOFER 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 MALTOFER³³⁻³⁴.

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 MALTOFER³⁵⁻³⁷. These results suggest that MALTOFER 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 the therapy with iron polymaltose.

MALTOFER

ADVERSE EFFECTS

Clinical Trials (Pre- and Post-authorisation, Including Post-authorisation Safety Studies)

The safety and tolerability of MALTOFER has been evaluated in numerous clinical trials and published reports³⁸. The principal adverse drug reactions that have been reported in these trials occurred in the three system organ classes:

Table 6. Adverse Drug Reactions Detected in Clinical Trials

| System Organ Class | Very Common (≥1/10) | Common (≥1/100, <1/10) | Uncommon (≥1/1,000, <1/100) | Rare (≥1/10,000, <1/1,000) | Very rare (< 1/10,000) |
|---|---------------------------------|------------------------------|--|----------------------------|------------------------|
| Gastrointestinal Disorders | discoloured faeces ¹ | diarrhoea, nausea, dyspepsia | vomiting, constipation, abdominal pain, tooth discoloration ² | | |
| Skin and Subcutaneous Tissue Disorders | | | rash, pruritus | | |
| Nervous System Disorders | | | headache | | |

1: Discoloured faeces were very commonly reported as an adverse event (23% of patients) and are a well-known ADR of oral iron medications.

2: Tooth Discoloration was reported as an adverse event in 0.6% of the patients and is a known ADR of oral iron medications.

Notes: "Exanthema" was combined with "rash" and presented as "rash" in the table.

Undesirable effects from post-marketing spontaneous reporting

No additional adverse drug reactions were identified.

Laboratory abnormalities

No data available

DOSAGE AND ADMINISTRATION

The dosage and duration of treatment depend upon the extent of iron deficiency. The daily dose can be divided into separate doses or can be taken at once. MALTOFER should be taken during or immediately after a meal.

Doses below 100 mg iron cannot be achieved with MALTOFER TABLETS. In cases where lower doses are required, MALTOFER oral liquids (SYRUP or DROPS) should be used.

MALTOFER tablets should be swallowed whole. Do not chew film-coated MALTOFER tablets.

MALTOFER oral liquids can be mixed with fruit and vegetable juices. The slight discoloration of the mixture does not affect either the taste of the juices or the efficacy of MALTOFER.

MALTOFER

Treatment of iron deficiency in adults and adolescents (children \geq 12 years):

100 mg to 200 mg iron (1 to 2 tablets, 10-20 mL syrup, or 40-80 drops) daily preferably with food, or higher doses as directed by a medical practitioner.

Prevention of iron deficiency in adults and adolescents (children \geq 12 years) at high risk:

100 mg iron (1 tablet, 10 mL syrup, 40 drops) daily preferably with food, or higher doses as directed by a medical practitioner.

Regular monitoring of haematological parameters and iron store levels are recommended to assess the patient's response to treatment.

OVERDOSAGE

Overdosage of iron causes haemosiderosis and consequent cirrhosis of the liver, diabetes and heart failure. Periodic monitoring of serum ferritin may be useful in recognizing a deleterious, progressive accumulation of iron.

Overdosage should be treated with supportive measures and, if required, an iron chelating agent.

For the information of the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

Presentations

MALTOFER TABLETS are available in pack sizes of 30 or 100 film-coated tablets packed in aluminium blister packs.

MALTOFER SYRUP Oral liquid is available in a 150 mL Type III brown glass bottle closed with a child resistant and tamper-evident screw cap. A measuring cup for administration covers the screw cap.

MALTOFER DROPS Oral liquid is available in a 30 mL Type III brown glass bottle with child resistant inserted dropper applicator and closed with a tamper-evident screw cap.

Storage conditions

Store below 25°C.

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

Note: Not all formulations of MALTOFER may be marketed in Australia.

NAME AND ADDRESS OF THE SPONSOR

Vifor Pharma Pty Ltd
Level 8, 80 Dorcas Street
South Bank, Melbourne VIC 3006
Australia

POISON SCHEDULE OF THE MEDICINE

S2 (Pharmacy medicine)

REFERENCES

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DATE OF INCLUSION ON THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (ARTG):

Maltofer Tablets: 22 October 2014
Maltofer Syrup: 14 November 2014
Maltofer Drops: 14 November 2014