NEW ZEALAND DATA SHEET

1 MALTOFER® 100 MG TABLETS AND 50 MG/5 ML SYRUP

MALTOFER® TABLETS 100 mg tablets

MALTOFER® SYRUP 50 mg/5 mL syrup

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

MALTOFER® TABLETS contains 100 mg iron as iron polymaltose as the active ingredient.

MALTOFER® SYRUP contains 50 mg/5 mL iron as iron polymaltose as the active ingredient.

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.

For the full list of excipients, see section 6.1 List of excipients.

Iron polymaltose is a polynuclear iron(III)-hydroxide core surrounded by polymaltose and has a molecular weight of about 50kD.

3 PHARMACEUTICAL FORM

MALTOFER® TABLETS are film-coated, reddish brown, round and biconvex tablets. Tablets cannot be halved.

MALTOFER® SYRUP, oral liquid is a dark brown solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic 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.

4.2 Dose and method of administration

Dose

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® SYRUP should be used.

Treatment of iron deficiency in adults and adolescents (adolescents ≥ 12 years):

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

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

100 mg iron (1 tablet or 10 mL syrup) 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.

Method of administration

MALTOFER® TABLETS should be swallowed whole. Do not chew film-coated MALTOFER® TABLETS. Do not halve the tablet.

MALTOFER® SYRUP can be mixed with fruit and vegetable juices. The slight discolouration of the mixture does not affect either the taste of the juices or the efficacy of MALTOFER®.

4.3 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)

4.4 Special warnings and precautions for use

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 haemachromatosis 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 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.

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.

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.

Effects on laboratory tests

MALTOFER® can cause discoloured (black) stool. Discoloured (black) stool may visually mask gastrointestinal bleeding. However, 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.

4.5 Interaction with other medicines and other forms of interaction

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

Interactions of iron polymaltose 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 bacteriostasis. Iron absorption from iron polymaltose was not reduced by aluminium hydroxide or tetracycline. Iron polymaltose 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 iron polymaltose .

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 iron polymaltose. These results suggest that iron polymaltose 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.

4.6 Fertility, pregnancy and lactation

Use in pregnancy (Category B1)

Medicines should only be prescribed in pregnancy if the expected benefits to the mother are considered to be greater than the risk to the mother and foetus.

Category B1: Medicines 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.

As a precautionary measure, women of childbearing age, and women during pregnancy should only use MALTOFER® after consulting a medical doctor or pharmacist. A benefit/risk evaluation is advisable.

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 period. 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 maturity.

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

Effects on fertility

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

4.7 Effects on ability to drive and use machines

Not relevant

4.8 Undesirable effects

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

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

The principal adverse drug reactions that have been reported in these trials occurred in the 4 system organ classes (see Table 1):

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, diarrhoea and abdominal pain).

Table 1: 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 (≥1/10,000, <1/1,000)
Gastrointestinal Disorders	Faeces discoloured[(1)]	Diarrhoea, nausea, abdominal pain[(2)], constipation	Vomiting[(3)], tooth discoloration , gastritis	
Skin and Subcutaneous Tissue Disorders			Pruritus, Rash[(5,6)], urticarial[(6)], erythema[(6)]	
Nervous System Disorders			Headache	
Musculoskeletal and connective tissue disorders				Muscle spasms[(4)], myalgia

1 Faeces discoloured were reported with less frequency in the meta-analysis, but is a well-known drug-related effect of oral iron therapy in general. Therefore it has been allocated to the very common frequency of undesirable effects.
2 Includes: abdominal pain, dyspepsia, epigastric discomfort, abdominal distension
3 Includes: vomiting, regurgitation
4 Includes: muscle contraction involuntary, tremor
5 Includes: rash, rash macular, rash vesicular
6 events originating from Post-Marketing Spontaneous Reporting, Estimated incidence of < 1/ 491 patients (upper limit of 95% confidence interval)

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.

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

In case of overdose, intoxication or iron accumulation are unlikely with Maltofer®. No cases of accidental poisoning with fatal outcome have been reported due to the low toxicity of iron polymaltose and controlled uptake of iron.

Acute overdose of iron polymaltose may cause headache, nausea, vomiting, diarrhoea, abdominal pain, lack of appetite or bloating.

In general, 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 National Poisons Centre (telephone 0800 POISON or 0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The polynuclear iron core of iron polymaltose is hypothesized to have a structure similar to that of the physiological iron storage protein ferritin. Iron polymaltose 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 polymaltose through the membrane of the mucosa is about 40 times less than that of most water soluble iron(II) salts, existing in aqueous solution as hexaqua-iron(II) ion complex. Iron from iron polymaltose is taken up in the gut via an active mechanism.

The intended pharmacological action of iron polymaltose is to provide utilisable iron to target tissues. Iron polymaltose is effective in delivering iron across enterocytes to the iron transport protein transferrin and the iron storage protein ferritin. This iron is subsequently incorporated into haemoglobin during synthesis of red blood cells and thus facilitates correction of iron deficiency and anaemia.

Chemical structure

Iron polymaltose, the active substance of MALTOFER®, is a macromolecular complex in which polynuclear iron(III)-hydroxide is stabilized by polymaltose. It contains about 53% mass fraction mass/mass (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

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 treatment. 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 Jacobs 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 peroxidation. All male subjects (n=45) with iron deficiency (serum ferritin ≤ 30 µg/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) (see Table 2). 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®) (see Table 2).

Table 2: Iron status (mean values) at baseline and following 6 months treatment; placebo vs MALTOFER® and ferrous sulfate (FS) vs placebo.

Treatment		Haemoglobin g/L; change (SEM)			Serum ferritin µg/L; change (SEM)			Erythrocyte ferritin µg/cell; change (SEM)		
	n	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: iron polymaltose vs Placebo; [2] P value: iron polymaltose 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 adults. 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 3. 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 3: Hb (g/dL) levels in "all patients" and per-protocol analyses; mean ± SD

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 investigated. 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 (see Table 4), 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 4: Changes in iron status from baseline to week 12 in the four treatment groups (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 al, 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 in Table 5.

Table 5:Results of Hb response over 12 weeks of treatment (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 adults.

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). Subjects were divided into 4 groups with 30 subjects/group: placebo, control supplement, iron deficient (Transferrin Saturation (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 (see Table 6). The greatest increase in Hb (+33 g/L) was seen in the IDA group. No gastrointestinal adverse effects were reported.

Table 6: Effects of MALTOFER® treatment in adolescents compared to placebo after 8 months of treatment (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.

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 inconclusive.

5.2 Pharmacokinetic properties

The iron of iron polymaltose is absorbed by a controlled mechanism in the small intestine and unabsorbed iron is excreted via faeces. After absorption, iron is transferred to the blood, where it is immediately bound to transferrin and distributed to the sites of demand, or stored as ferritin in liver and spleen. Most iron is incorporated into the oxygen-transport protein haemoglobin (Hb) during erythropoiesis in the bone marrow. The iron from erythrocytes is recycled at the end of their life span. The breakdown products of polymaltose (maltose and gluconate) are converted into glucose which is metabolised.

Studies with radiolabelled iron polymaltose showed a good correlation between iron absorption (quantified by whole body count) and the iron incorporation into Hb. Similar to other oral iron preparations, the relative absorption of iron decreases with increasing doses. The relative amount of

absorbed iron correlates positively with the extent of iron deficiency (i.e., the higher the iron deficiency, the better the relative absorption). No negative impact of food on the bioavailability of iron from iron polymaltose was found: A significantly increased bioavailability of iron (7.3 fold) with concomitant food intake was demonstrated in one clinical study, while 3 studies showed a positive trend (1.1 to 2.1 fold increased bioavailability) but no clinically relevant effects.

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.

Carcinogenicity

No long-term studies of tumourigenic potential are available.

Genotoxicity

Iron polymaltose was not genotoxic in a conventional battery of *in vitro* and *in vivo* tests.

Teratogenicity

Embryo-foetal toxicity studies of iron polymaltose in animals did not reveal any foetal risk . Treatment of rats and rabbits with iron polymaltose during organogenesis did not induce any teratogenic or embryolethal effects. Based on these animal studies, there is no evidence of a risk during the first trimester.

No effects of iron polymaltose on the pre- and post-natal development of offspring were observed in a study in rats, in which dams were treated from Day 6 after mating to Day 20 of lactation, inclusive.

Other

The LD_{50} for iron polymaltose, as determined in animal studies with mice or rats was greater than an orally administered dose of 2,000 mg of iron per kilogram body weight. The available nonclinical data on toxicity after a single dose and repeated administration have yielded no further information that has not already been mentioned in other sections.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The tablets also contain crospovidone, hydroxypropylcellulose, hypromellose, iron oxide red, iron oxide yellow, macrogol 6000, magnesium stearate, cellulose - microcrystalline and titanium dioxide.

The oral solution also contains cream flavour, ethanol, methyl hydroxybenzoate, propyl hydroxybenzoate, water - purified, sodium hydroxide, sorbitol solution (70%) (non-crystallising), and sucrose.

6.2 Incompatibilities

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.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25°C.

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

6.5 Nature and contents of container

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.

Note: Not all formulations of MALTOFER® may be marketed.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Pharmacy Only

8 SPONSOR

Pharmacy Retailing
(trading as Healthcare Logistics)
58 Richard Pearce Drive,
Airport Oaks
Mangere
Auckland 2022
New Zealand

9 DATE OF FIRST APPROVAL

7 June 2018

10 DATE OF REVISION OF THE TEXT

6 February 2023

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Footer updated with date and product name throughout the data sheet. Other minor editorial and formatting changes.