Tiptipot Ferripel-3, oral drops
Ferripel-3 Syrup, per os

Active substance

Tiptipot Ferripel-3 contains 50 mg/ml iron as iron (III) hydroxide polymaltose complex (IPC)

Ferripel-3 Syrup contains 50mg/5ml iron as iron (III) hydroxide polymaltose complex (IPC)

Indications

Prevention and treatment of anaemia caused by iron deficiency

Excipients

Ferripel-3 Syrup

Sorbitol solution 70%, Sucrose, Ethanol 96%, Cream Essence, Methyl hydroxybenzoate, Propyl hydroxybenzoate, Sodium hydroxide, Dilute hydrochloric acid, Purified water.

Tiptipot Ferripel-3

Sucrose, Cream Essence, Sodium Methyl Hydroxybenzoate, Sodium Propyl Hydroxybenzoate, Sodium Hydroxide, Dilute Hydrochloric Acid, Purified Water

Posology/Administration

Ferripel-3 syrup
Adults and children above 12 years of age:
For prevention of anaemia: 1-2 teaspoons per day
For treatment of anaemia: 2-4 teaspoons per day

Dosage for children:
For prevention of anaemia: 1 mg (0.1ml)/kg body weight per day
For infants up to the age of 2 years do not exceed a dosage of 15 mg per day.
For treatment of anaemia: up to 2 mg (0.2ml)/kg body weight 3 times a day.

Tiptipot Ferripel-3
Adults and children above 12 years of age:
For prevention of anaemia: 15-30 drops per day
For treatment of anaemia: 45-60 drops per day

Dosage for children:
For prevention of anaemia: 1 mg iron/kg body weight per day
For infants up to the age of 2 years do not exceed a dosage of 15 mg per day.
Premature babies: 2.5-5 mg (1-2 drops)/kg body weight per day.

According to the Family Health Center recommendations – use the table below that lists the dosages according to the child's age.

Child's age	Required dose in drops	Required dose in mg per day
Age 4 months and above	3	Approx.. 7 mg
Age 6 months and above	6	15 mg

For treatment of anaemia: up to 6 mg iron (2 drops)/kg body weight per day.

The daily dose can be divided into individual doses or administered all at once. The Ferripel-3 syrup and Tiptipot Ferriple-3 preparations should be taken with or directly after meals.
The Ferripel-3 syrup and Tiptipot Ferriple-3 can be mixed with fruit or vegetable juices or with bottle feed. The slight discolouration does not impair the effect or the taste.
In order to ensure the accurate dosing of Tiptipot Ferripel-3, the bottle must be held upside down and vertically. A drop will form immediately at the end of the dropper bottle. If this is not the case, tap the bottle gently until a drop forms. Do not shake the bottle.

Contraindications

- Known hypersensitivity to or intolerance of the active substance iron (III) hydroxide polymaltose complex or one of the excipients,
- Iron overload (e.g. haemochromatosis, haemosiderosis),
- Iron metabolism disorders (lead anaemia, sideroachrestic anaemia, thalassaemia),
- Any anaemia not caused by iron deficiency (e.g. haemolytic anaemia or megaloblastic anaemia caused by vitamin B_{12} deficiency).

Special warnings and precautions

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. Caution is recommended in patients who receive repeated blood transfusions, as there is a supply of iron with erythrocytes, which can lead to iron overload.
Treatment with Ferripel-3 syrup and Tiptipot ferripel-3 can cause dark discolouration of the faeces (stool) but this has no clinical significance.
Infections or tumours can cause anaemia. As oral iron can be utilised only after the primary disease has been treated, a benefit/risk analysis is indicated.

Tiptipot Ferripel-3 contains 0.29 mg/ ml of sodium.

Tiptipot Ferripel-3 contain sodium methyl hydroxybenzoate and sodium propyl hydroxybenzoate. These can cause allergic reactions, even delayed reactions.

Tiptipot Ferripel-3 contain 50mg/ml sucrose: 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.

Ferripel-3 syrup contains sodium.

Ferripel-3 syrup contains 2000 mg/5 ml of sorbitol 70%. Sorbitol can cause gastrointestinal disorders and has a slight laxative effect. Patients with hereditary fructose intolerance (HFI) should not take/receive this medicinal product.

Ferripel-3 syrup contains 1000 mg/5 ml of sucrose. Diabetes patients must take this into account. Sucrose can be harmful to the teeth.

Ferripel-3 syrup contains small quantities of ethanol (alcohol) of less than 100 mg per 30 mL (maximum daily dose).

Ferripel-3 syrup contains methyl hydroxybenzoate and propyl hydroxybenzoate. These can cause allergic reactions, even delayed reactions.

Interactions

Interactions of the iron (III) hydroxide polymaltose complex with tetracycline or aluminium hydroxide were investigated in three human studies (cross-over design, 22 patients per study). No significant reduction in the absorption of tetracycline was shown. The plasma concentration of tetracycline did not fall below the level necessary for efficacy. The absorption of iron from iron (III) hydroxide polymaltose complex was not reduced by aluminium hydroxide and tetracycline. The iron (III) hydroxide polymaltose complex can therefore also be administered at the same time as tetracyclines or other phenolic compounds, as well as aluminium hydroxide.
Studies in rats with tetracycline, aluminium hydroxide, acetylsalicylate, sulfasalazine, calcium carbonate, calcium acetate, calcium phosphate in combination with vitamin D3, bromazepam, magnesium aspartate,
D-penicillinamine, methyldopa, paracetamol and auranofin have not shown any interactions with the iron (III) hydroxide polymaltose complex.
There were also no interactions of the iron (III) hydroxide polymaltose complex with food components, such as phytic acid, oxalic acid, tannin, sodium alginate, choline and choline salts, vitamin A, vitamin D3 and vitamin E, soy oil and soy flour observed in in-vitro studies. These results indicate that iron (III) hydroxide polymaltose complex can be taken during or immediately after food intake.
The haemoccult test (selective for Hb) for the detection of occult blood is not affected; the therapy therefore must not be interrupted.
The concomitant administration of parenteral iron preparations and Ferripel-3 (Tiptipot Ferripel-3 and Ferripel-3 syrup) is not indicated as the absorption of the oral iron preparation would be inhibited and parenteral iron preparations may only be used if oral treatment is not suitable.

Pregnancy, lactation

Pregnancy

Clinical data of exposed pregnancies exhibited no undesirable effects on pregnancy or on the health of the foetus or newborn infant (see Properties/Effects).
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, Ferripel-3 syrup and Tiptipot ferripel-3 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, Ferripel-3 syrup and Tiptipot ferripel-3should 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 Ferripel-3 syrup and Tiptipot ferripel-3has any effect on the ability to drive and use machines.

Undesirable effects

The frequency of the undesirable effects described below is divided into very common (≥1/10), common (<1/10 to ≥1/100), uncommon (<1/100 to ≥1/1,000) or rare (<1/1,000).

The safety and tolerability of Ferripel-3 syrup and Tiptipot Ferripel-3 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).
Stool discolouration 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).

Gastrointestinal disorders

Very common: Stool discolouration*.

Common: Diarrhoea, nausea, abdominal pain (including: abdominal pain, dyspepsia, epigastric discomfort, abdominal distension), constipation.

Uncommon: Vomiting (including: vomiting, regurgitation), teeth discolouration, gastritis.

Skin and subcutaneous tissue disorders

Uncommon: pruritus, rash (including: rash, macular rash, bullous rash)**, urticaria**, erythema**.

Nervous system disorders

Uncommon: headache

Musculoskeletal and connective tissue disorders

Rare: 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).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il/

Overdose

In the case of overdoses, an intoxication or iron accumulation is unlikely due to the low toxicity of the iron (III) hydroxide polymaltose complex (in mice and rats, the 50% lethal dose (LD50) is >2000 mg Fe/kg of body weight) and the expected saturation of iron uptake. No cases of accidental poisoning with fatal outcome are known.

Properties/Effects

ATC code
B03AB05

Mechanism of action

The polynuclear iron (III) hydroxide core in IPC is surrounded at its surface by a number of non-covalently bound polymaltose molecules, which leads to an average total molecular weight of around 50 kDa. The polynuclear iron core of IPC has a structure similar to that of the physiological iron storage protein ferritin. IPC is a stable complex and releases no large quantities of iron under physiological conditions. Due to its size, the magnitude of IPC diffusion taking place through the mucosa is around 40 times less than in most water-soluble iron (II) salts present in aqueous solution as a hexaaqua-iron (II) complex. Iron is absorbed in the intestines from IPC through an active mechanism.

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 Ferripel-3 syrup and Tiptipot Ferripel-3 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 Ferripel-3 syrup and Tiptipot Ferripel-3in children and adolescents (18 years old or younger) was investigated in a number of clinical studies involving over 1000 patients. The efficacy of Ferripel-3 syrup and Tiptipot ferripel-3in 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 Ferripel-3 syrup and Tiptipot ferripel-3: 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.

Shelf life

The expiry date of the product is indicated on the packaging materials.

Special storage instructions

Store below 25°C, in a dark place.
Ferripel-3 Syrup may be used up to a month after first opening.
Tiptipot Ferripel-3 may be used up to 3 months after first opening.

Registration number of the medicine in the national registry of the Ministry of Health

Ferripel-3 syrup: 1074728826-00
Tiptipot ferripel-3: 1074628828-00

Packs
Tiptipot Ferripel-3: 15 mL
Ferripel-3 Syrup: 110 mL

Manufacurer/Marketing Authorisation Holder
CTS Chemical Industries Ltd. 3 Hakidma St, Kiryat Malachi.

The content of this leaflet was updated according to the guidelines of the Ministry of Health in 12/2020