Ferrifol Tablets, per os

Active substances

Ferrifol tablets contain 100 mg Iron as iron III hydroxide polymaltose complex and 0.4 mg folic acid.

Indications

Prevention and treatment of anaemia caused by iron and folic acid deficiency including anaemia of pregnancy and lactation.

Excipients

Ferrifol tablets contain: Dextrates, Polyethylene Glycol 6000, Purified Talc, Aspartame, Magnesium Stearate, Chocolate Essence

Posology/Administration

Adults and children above 12 years of age:
For prevention of anaemia: one tablet per day.
For treatment of anaemia: 3 tablets per day taken as one daily dose or as separate doses.

Ferrifol tablets should be taken with or directly after meals and can be chewed or swallowed whole.

Paediatric Population

Ferrifol tablets are not indicated for children and adolescents below 12 years of age.

Contraindications

- known hypersensitivity to or intolerance of the active substances 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 B12 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.
Ferrifol contains folic acid which can mask a vitamin B12 deficiency. A potential vitamin B12 deficiency must be ruled out before the start of treatment in anaemic patients due to the risk of irreversible neurological dysfunctions, see "Contraindications".

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

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.
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.

Interactions

Interactions of the iron (III) hydroxide polymaltose complex (IPC) 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 bacteriostasis. The absorption of iron from IPC 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 impaired, and therefore there is no need to interrupt the therapy.
Concomitant administration of parenteral iron preparations and Ferrifol is not indicated because it would reduce the absorption of the oral iron preparation.
Folic acid could increase the metabolism of phenytoin resulting in decreased concentrations of phenytoin in the serum, particularly in patients with folic acid deficiency. There may be an increased frequency of epileptic seizures in some patients. Patients who take phenytoin or another antiepileptic/anticonvulsive medicinal product should consult a doctor before taking a folic acid supplement.
There are reports that the concurrent administration of chloramphenicol and folic acid in patients with folic acid deficiency may result in antagonism of the haematopoietic response to folic acid. Although the importance and mechanism of this interaction is unclear, the haematopoietic response to

folic acid in patients taking both medicinal products concomitantly should be carefully monitored.

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, Ferrifol 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, Ferrifol 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. It is unlikely that Ferrifol has any effect on the ability to drive and use machines.

Undesirable effects

The frequency of the undesirable effects described below is classified 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 Ferrifol has been evaluated by meta-analysis of 24 literature articles 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 4 system organ classes (see below).

Discoloured faeces are a well-known adverse drug reaction of oral iron medications, but this is considered of no clinical relevance and is frequently underreported. Other commonly seen side effects were gastrointestinal disorders (nausea, constipation, diarrhoea, and abdominal pain).

Gastrointestinal disorders

Very common: discoloured faeces*

Common: diarrhoea, nausea, abdominal pain (includes: abdominal pain, dyspepsia, epigastric discomfort, abdominal distension), constipation
Uncommon: vomiting (includes: vomiting, regurgitation), tooth discolouration, gastritis

Skin and subcutaneous tissue disorders

Uncommon: pruritus, rash (includes: rash, rash macular, rash vesicular)**, urticarial**, erythema**

Nervous system disorders

Uncommon: headache

Musculoskeletal ,connective tissue and bone disorders

Rare: Muscle spasms (includes: involuntary muscle contraction, tremor), Myalgia

* Discoloured faeces 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.
** events originating from Post-Marketing Spontaneous Reporting, 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 are unlikely due to the low toxicity of the iron (III) hydroxide polymaltose complex (in mice and rats the 50% lethal dose (LD_{50}) 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.
There are reports that an excessive dose of folic acid may cause changes to the central nervous system (namely changes in mental state, changes to the sleep pattern, irritability and hyperactivity), nausea, abdominal distension and flatulence.

Properties/Effects
ATC code B03AD04

Mechanism of action/Pharmacodynamics

In IPC, the polynuclear iron (III) hydroxide core is surrounded at its surface 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 most water-soluble iron (II) salts, existing in aqueous solution as Hexaquo-iron(II) ion complex. Iron from the complex IPC is taken up in the gut via an active mechanism.
Folic acid (folate) is a member of the Vitamin B group. It is a tetrahydrofolate precursor, a coenzyme involved in various metabolic processes including the biosynthesis of nucleic acid purines and thymidylates. Folic acid is required for nucleoprotein synthesis and maintenance of normal erythropoiesis.
The absorbed iron is bound to transferrin and is used for Hb synthesis in the bone marrow or is stored, mainly in the liver, where it is bound to ferritin.

Clinical efficacy

During pregnancy, there is an increased requirement for iron which is approximately 0.8 mg/day in the first trimester and up to 6 mg/day during the third trimester of pregnancy. In addition, there is an increased requirement for folic acid, particularly during pregnancy. Low folic acid levels can lead to signs of deficiency in both mothers (anaemia, peripheral neuropathies) and the foetus (congenital neural tube defects).

Clinical studies have been carried out in pregnant women to investigate the safety and efficacy of the treatment of iron deficiency with or without anaemia, as well as to prevent an iron and folic acid deficiency with IPC treatment in combination with folic acid (Ferrifol). Changes in haematological parameters were compared during treatment with Ferrifol tablets at a dose of 100 mg–300 mg iron/day in conjunction with 0.35 mg folic acid/day in comparison to iron (II) sulphate standard preparations with and without folic acid. A study investigated the efficacy of IPC with the addition of a folic acid supplement compared to intravenous

iron administration, and another study examined the efficacy and tolerability of Ferrifol compared to a diet high in iron. In total, approximately 700 pregnant women with normal and decreased iron were included, and more than 400 of these patients received Ferrifol.

Treatment of pregnant women with Ferrifol showed similar improvements in haematological parameters compared to results with Ferrifol in non-pregnant patients with at the same time a good tolerability. An improvement in the haemoglobin values to an average of 0.72 to 2.2 g/dL ($p<0.05$) as compared to the start of treatment was observed in the clinical studies following treatment with Ferrifol lasting between 30 days and 2.5 months. In addition, improvements were measured in serum ferritin (+5.74 mcg/L) and in red blood cell ferritin levels (on average +6.3 mcg/g or 5.74 mcg/g after treatment lasting 30 days or 2.5 months compared to the baseline). An open study investigated the efficacy of Ferrifol (200 mg IPC/day for 10 days and 100 mg/day for 20 days) with supplemental vitamin B12 in pregnant women with iron deficiency anaemia. There was a significant increase in haemoglobin values as well as in the haematocrit, the number of erythrocytes and folic acid values. ($p<0.01$).

An open study with 43 young adults with varying degrees of iron deficiency anaemia between the ages of 14.5 and 17 years investigated the efficacy of Ferrifol on haemoglobin levels. Changes in the Hb values after 48 to 49 days of treatment compared to the baseline were 10.44 ±0.08 g/dL, 11.64 ±0.07 g/dL and 13.41 ±0.13 g/dL with mild, moderate or severe anaemia, and after 75 to 76 days of treatment 13.32 ±0.11 g/dL and 12.64 ±0.07 g/dL (moderate and severe anaemia).

Pharmacokinetics

Absorption

Studies with radioactive-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). Unlike iron (II) salts, no negative

Effects of food on the bioavailability of iron from Ferrifol were identified:
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.
Around 80% of folic acid is absorbed in the small intestine, with maximum absorption occurring after 30–60 minutes.

Elimination

Iron that is not absorbed is excreted in the faeces. Folic acid is mainly excreted in the urine.

Preclinical data

Nonclinical data done with IPC revealed no special hazard for humans, based on conventional studies of single dose and repeated dose toxicity, genotoxicity, and reproductive and developmental toxicity.

Other information

The LD50 for IPC, 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.

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.

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

131-01-30647- 00

Packaging

Packages of 20 or 30 tablets.

Manufacturer/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