For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

Herfem
(Ferrous Ascorbate, Folic Acid & Zinc Tablets)

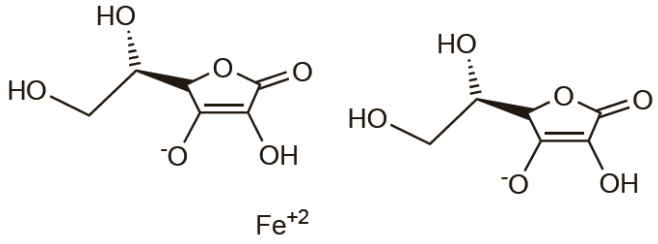
COMPOSITION

Each film coated tablet contains:
Ferrous Ascorbate equivalent to
Elemental Iron 100mg
Folic Acid I.P.....1.5mg
Zinc Sulphate Monohydrate I.P. equivalent to
Elemental Zinc 22.5mg
Excipients .....q.s.
Colors: Red Oxide of Iron & Titanium Dioxide I.P.
(Appropriate overages added for vitamin)

DESCRIPTION

Ferrous Ascorbate

Ferrous Ascorbate is used as a source of iron for iron deficiency anaemia. The empirical formula of Ferrous Ascorbate is $C_{12}H_{14}FeO_{12}$ and its molecular weight is 406.1.

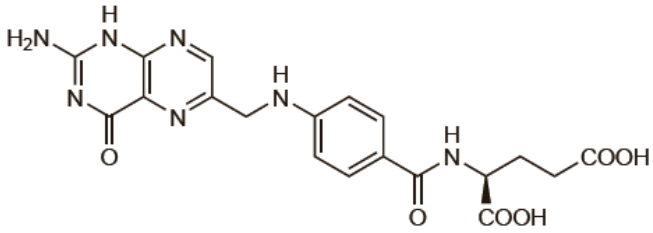


Zinc Sulphate

Zinc Sulphate is $ZnSO_4,7H_2O$ and its molecular weight is 287.5.

Folic Acid

Folic acid is a member of the vitamin B group. It is used in the treatment and prevention of folate deficiency states. Folic Acid is $C_{19}H_{19}N_7O_6$ and its molecular weight is 441.4.



CLINICAL PHARMACOLOGY

Pharmacokinetics

Ferrous Ascorbate

Iron is irregularly and incompletely absorbed mainly from duodenum and jejunum. Its absorption is enhanced by haem complex form, acidity, in fasting and iron deficiency state and its decreases if the body stores are overloaded

Most absorbed iron is bound to transferrin and transported to the bone marrow where it is incorporated into haemoglobin; the remainder is contained within the storage forms, ferritin or haemosiderin, or as myoglobin, with smaller amounts occurring in haem containing enzymes or in plasma bound to transferrin. Only very small amounts of iron are excreted as the majority released after the destruction of the haemoglobin molecule is re-used.

Zinc Sulphate

Absorption of zinc from the gastrointestinal tract is incomplete, and is reduced in the presence of some dietary constituents such as phytates. Bioavailability of dietary zinc is about 20 to 30%. Zinc is distributed throughout the body with the highest concentrations found in muscle, bone, skin, eye, and prostatic fluids. It is primarily excreted in the faeces, and regulation of faecal losses is important in zinc homoeostasis. Small amounts are lost in urine and perspiration.

Folic Acid

Absorption – folic acid is rapidly absorbed from the gastrointestinal tract, mainly from the proximal part of the small intestine. Folic acid given therapeutically enters the portal circulation largely unchanged, since it is a poor substrate for reduction by dihydrofolate reductases.

Distribution – via portal circulation. 5MTHF from naturally occurring folate is extensively plasma bound. The principal storage site of folate is in the liver; it is also actively concentrated in the CSF. Folate is distributed into breast milk.

Metabolism – therapeutically given folic acid is converted into the metabolically active form 5MTHF in the plasma and liver. There is an enterohepatic circulation for folate.

Elimination – Folate metabolites are eliminated in the urine and folate in excess of body requirements is excreted unchanged in the urine. Folic acid is removed by haemodialysis.

INDICATIONS

For the treatment of iron deficiency anaemia

Human Requirements

Ferrous Ascorbate

A dietary allowance containing the equivalent of about 10 mg of iron daily is usually sufficient for men and postmenopausal women; up to 15 mg daily may be necessary for premenopausal women with normal menstrual blood losses.

Zinc Sulphate
They recommend an upper limit of the safe range of population mean intakes of zinc of 35 mg daily for women, and 45 mg daily for men.

Folic Acid
150 to 200 micrograms of folate daily is considered a suitable average intake for all healthy persons except women of child-bearing potential and pregnant women who require additional folic acid to protect against neural tube defects in their off spring.

CONTRAINDICATION

Folic Acid
• Long-term folate therapy is contraindicated in any patient with untreated cobalamin deficiency or Addisonian pernicious anaemia because it may precipitate the onset of subacute combined degeneration of the spinal cord..

• Folic acid should not be used in malignant disease unless megaloblastic anaemia owing to folate deficiency is an important complication.

• Known hypersensitiviy to the active ingredient or any of the excipients.

WARNINGS AND PRECAUTIONS

Ferrous Ascorbate
Iron compounds should not be given to patients in following conditions

- Receiving repeated blood transfusions or to patients with anaemias not produced by iron deficiency.
- Already parenteral iron therapy continue.
- Iron-storage or iron-absorption diseases such as haemochromatosis, haemoglobinopathies
- Existing gastrointestinal diseases such as inflammatory bowel disease, intestinal strictures and diverticulae.
- Non-deficient subjects because increased risk of microbial infection after supplementation, in children without iron deficiency may retard their growth,.iron may be associated with ischaemicheart disease, by modifying low-density lipoprotein in ways which increase its atherogenic potential and by sensitising the myocardium to ischaemic injury.

Folic Acid
Patients with rare hereditary problems of galactose intolerance, the lapp lactase deficiency or glucose - galactose malabsorption should not take this medicine and caution should be exercised to patients who may have folate dependent tumours.

DRUG INTERACTION

Ferrous Ascorbate
Compounds containing calcium and magnesium, including antacids and mineral supplements, and bicarbonates, carbonates, oxalates, or phosphates, tetracyclines, trientine, acetohydroxamic acid, chloramphenicol, levothyroxine, cefdinir,

bisphosphonates, entacapone, fluoroquinolones, levodopa, methyldopa, mycophenolate mofetil, and penicillamine and Zinc salts may impair the absorption of iron. Some agents, such as ascorbic acid and citric acid, may actually increase the absorption of iron. Iron should not be given with dimercaprol as toxic complexes may form.

Zinc Sulphate
The absorption of zinc may be reduced by iron supplements, penicillamine, phosphorus-containing preparations, and tetracyclines. Zinc supplements reduce the absorption of copper, fluoroquinolones, iron, penicillamine, and tetracyclines.

Folic Acid
Antiepileptics (phenytoin, phenobarbital and primidone), the serum antiepileptic levels may fall, Antibacterials (chloramphenicol and co-trimoxazole) may interfere with folate metabolism. Sulfasalazine - can reduce the absorption of folic acid. Folic acid may interfere with the toxic and therapeutic effects of methotrexate.

ADVERSE EFECTS

Ferrous Ascorbate
Gastrointestinal irritation and abdominal pain with nausea and vomiting, diarrhoea or constipation and black colored stool. Adverse effects can be reduced by giving it with or after food (rather than on an empty stomach) or by beginning therapy with a small dose and increasing gradually.

Zinc Sulphate
Gastrointestinal effects like abdominal pain, dyspepsia, nausea, vomiting, diarrhea, gastric irritation, and gastritis. These are particularly common if zinc salts are taken on an empty stomach, and may be reduced by giving them with meals. Prolonged use of high doses of zinc supplements leads to copper deficiency with associated sideroblastic anaemia, leucopenia and neutropenia.

Folic Acid

Gastrointestinal disorders Rare (1/10,000 til <1/1,000)	Anorexia, nausea, abdominal distension and flatulence
Immune system disorders Rare (1/10,000 til <1/1,000)	Allergic reactions, comprising erythema, rash, pruritus, urticaria, dyspnoea, and anaphylactic reactions (including shock).

OVERDOSAGE

Ferrous Ascorbate
Acute overdose
In treating acute iron poisoning, speed is essential to reduce absorption of iron from the gastrointestinal tract. Activated charcoal is ineffective, but gastric lavage should be considered in those who have ingested the equivalent of more than 60 mg/kg of elemental

iron within 1 hour of presentation. Serum-iron concentrations may be an aid to estimating the severity of poisoning.

Chronic Overdose
Because the body lacks a mechanism for the excretion of excess iron, abnormally high absorption or repeated blood transfusion will result in iron overload, leading eventually to haemochromatosis. The consequences of haemochromatosis include pigment deposition in skin and other organs, mild liver dysfunction, endocrine dysfunction (failure of the adolescent growth spurt, hypogonadism, ischaemic heart disease sometimes diabetes and hypothyroidism), and heart disease (pericarditis, heart failure, and arrhythmias). Where iron overload is due to increased absorption, phlebotomy is the treatment of choice; however, if phlebotomy is not tolerated or in patients who are transfusion-dependent (as in β-thalassaemia) treatment with iron chelators such as desferrioxamine is used to retard accumulation.

Zinc Sulphate
In acute overdosage zinc salts are corrosive, due to the formation of zinc chloride by stomach acid; treatment consists of giving milk or alkali carbonates and activated charcoal. The use of emetics or gastric lavage should be avoided.

Folic Acid
No special procedures or antidote are likely to be needed.

DOSAGES AND ADMINISTRATION

Ferrous Ascorbate
The usual adult dose for the treatment of iron deficiency anaemia is 100 to 200 mg of iron daily in divided doses. The usual adult prophylactic dose is about 60 to 120 mg of iron daily. Children's doses are up to 2 mg/kg of iron three times daily for treatment and 1 to 2 mg/kg daily for prophylaxis of iron-deficiency anaemia (usually to a maximum of 30 mg) has been used. Therapy is generally continued until haemoglobin concentrations reach normal values, which may take some weeks, and then for a further 3 months or more to restore body-iron stores.

Zinc Sulphate
In deficiency states, zinc is usually given orally as the sulfate, the sulfate monohydrate, or the gluconate, in doses of up to 50 mg of elemental zinc three times daily. The usual adult dose is 50 mg three times daily up to a maximum of five times daily. Children from 1 to 6 years may be given 25 mg twice daily; those from 6 to 16 years and with a body-weight under 57 kg are given 25 mg three times daily. Adolescents from 16 years of age, or with a body-weight of above 57 kg are given 50 mg three times daily. An effective dose in pregnant women is usually 25 mg three times daily; however, dosage is adjusted based on copper concentrations.

Folic Acid
In folate deficient megaloblastic anaemia: 5 mg daily for 4 months; up to 15 mg daily may be necessary for malabsorption states. In drug induced folate deficiency: 5 mg daily

for 4 months; up to 15mg daily may be necessary for malabsorption states. For prophylaxis in chronic haemolytic states or in renal dialysis: 5mg every 1-7 days depending on underlying disease. Prevention of neural tube defects in women known to be at risk: 5mg daily started before conception and continued throughout the first trimester.

USE IN PREGNANCY AND NURSING MOTHER
PREGNANCY
Zinc Sulphate
Zinc requirements are increased in pregnancy. Although it is unclear to what extent this has clinical consequences, some have suggested that supplementation with modest doses of zinc (less than 45 mg daily) during pregnancy may have beneficial effects on fetal growth and development, and lead to improved pregnancy outcomes.

Folic Acid
There are no known hazards to the use of folic acid in pregnancy; supplements of folic acid are often beneficial. Non-drug - induced folic acid deficiency, or abnormal folate metabolism, is related to the occurrence of birth defects and some neural tube defects. Interference with folic acid metabolism or folate deficiency induced by drugs such as anticonvulsants and some antineoplastics early in pregnancy results in congenital anomalies

LACTATION
Folic Acid
Folic acid is actively excreted in human breast milk. Accumulation of folate in milk takes precedence over maternal folate needs. Levels of folic acid are relatively low in colostrum but as lactation proceeds, concentrations of the vitamin rise. No adverse effects have been observed in breast fed infants whose mothers were receiving folic acid.

EXPIRY DATE:
Do not use later than the date of expiry.

STORAGE:
Store in a dry & dark place at a temperature not exceeding 25°C.

PRESENTATION
Herfem is available as Blister pack of 10 tablets

MARKETED BY:

TORRENT PHARMACEUTICALS LTD.
Torrent House, Off Ashram Road,
Ahmedabad-380 009, INDIA