

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

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**HERFEM PLUS (Ferrous Ascorbate, Folic Acid, Mecobalamin & Zinc Sulphate Tablets)**

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**COMPOSITION**

Each film coated tablet contains:

Ferrous Ascorbate equivalent to

Elemental Iron .....100mg

Folic Acid I.P..... 1.1mg

Mecobalamin I.P.....1500 mcg

Zinc Sulphate Monohydrate I.P. equivalent to

Elemental Zinc .....22.5mg

Excipients .....q.s.

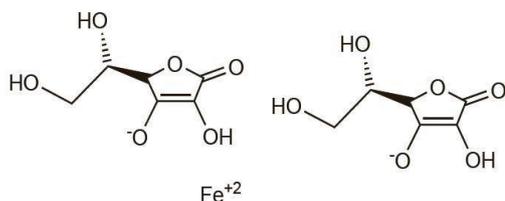
Colours: Red Oxide of Iron & Titanium Dioxide I.P.

Appropriate overages of vitamins are added.

**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.

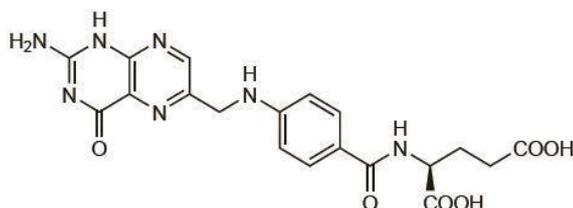


**Zinc Sulphate**

Zinc Sulphate is  $ZnSO_4 \cdot 7H_2O$  and its molecular weight is 287.5. Zinc Acts as an integral part of several enzymes important to protein and carbohydrate metabolism, wound healing, maintenance of normal growth and skin hydration, and senses of taste and smell. Folic

**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.



### **Mecobalamin**

Mecobalamin is a cobalamin, a form of vitamin B. It differs from cyanocobalamin in that the cyanide is replaced by a methyl group. Mecobalamin features an octahedral cobalt centre. Mecobalamin can be obtained as bright red crystals. Mecobalamin is equivalent physiologically to vitamin B<sub>12</sub>, and can be used to prevent or treat pathology arising from a lack of vitamin B<sub>12</sub> (vitamin B12 deficiency), such as pernicious anemia.

### **DOSAGE FORM**

Film coated tablets

### **INDICATIONS**

For the treatment of iron deficiency anaemia

### **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. Oral zinc salts, commonly the acetate, may be used as copper absorption inhibitors in Wilson's disease. 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: 5mg daily for 4 months; up to 15mg daily may be necessary for malabsorption states. In drug induced folate deficiency: 5mg 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.

#### **Mecobalamin**

The usual dose is 3 tablets (1.5 mg) daily in three divided doses. The dose may be adjusted depending on the patient's age and severity of symptoms.

## **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

### **Mecobalamin**

Mecobalamin is not recommended in pregnancy.

## **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.

### **Mecobalamin**

Mecobalamin is not recommended in lactation.

## **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 hypersensitivity 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 continues.
- 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 ischaemic heart 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.

Folic acid should never be given alone or with inadequate amounts of vitamin B12 for the treatment of undiagnosed megaloblastic anaemia, since folic acid may produce a haematopoietic response in patients with a megaloblastic anaemia due to vitamin B12 deficiency without preventing aggravation of neurological symptoms. This masking of the true deficiency state can lead to serious neurological damage, such as subacute combined degeneration of the spinal cord.

### **Mecobalamin**

**High numbers of red blood cells (polycythemia vera):** The treatment of vitamin B12 deficiency can unmask the symptoms of polycythemia vera.

**Abnormal red blood cells (megaloblastic anemia):** Megaloblastic anemia is sometimes corrected by treatment with vitamin B12. However, this can have very serious side effects. Don't attempt vitamin B12 therapy without close supervision by your healthcare provider.

**Leber's disease, a hereditary eye disease:** Do not take vitamin B12 if you have this disease. It can seriously harm the optic nerve, which might lead to blindness.

**Allergy or sensitivity to cobalt or cobalamin:** Do not use vitamin B12 if you have this condition.

**Post-surgical stent placement:** Avoid using a combination of vitamin B12, folate, and vitamin B6 after receiving a coronary stent. This combination may increase the risk of blood vessel narrowing.

## **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, methyl dopa, 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.

### **Mecobalamin**

Metformin, H<sub>2</sub> receptor antagonists (Cimetidine, Ranitidine etc), Aminoglycosides, Colchicine, Aminosalicic Acid, Anticonvulsants and Alcohol decrease absorption of Vitamin B<sub>12</sub>.

Vitamin B<sub>12</sub> is important for producing new blood cells. Chloramphenicol might decrease new blood cells. Taking chloramphenicol for a long time might decrease the effects of vitamin B<sub>12</sub> on new blood cells. But most people only take chloramphenicol for a short time so this interaction isn't a big problem.

## **ADVERSE EFFECTS**

### **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**

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

### **Mecobalamin**

Generally mecobalamin is well tolerated. However, a few side effects like gastrointestinal discomfort (including anorexia, nausea or diarrhea) may be seen after administration.

## **OVERDOSAGE**

### **Ferrous Ascorbate**

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). If unchecked, the iron build-up can lead to death, mainly through heart failure or arrhythmia. 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  $\beta$ -thalassaemia) treatment with iron chelators such as desferrioxamine is used to retard accumulation. 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.

### **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.

### **Mecobalamin**

Mecobalamin has excellent tolerability and no known toxicity. Treatment is unlikely to be needed in cases of over dose.

## **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 homeostasis. 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.

### **Mecobalamin**

Mecobalamin is the neurologically active form of vitamin B12 and occurs as a watersoluble vitamin in the body. It is a cofactor in the enzyme methionine synthase, which functions to transfer methyl groups for the regeneration of methionine from homocysteine. In anaemia, it increases erythrocyte production by promoting nucleic acid synthesis in the bone marrow and by promoting maturation and division of erythrocytes.

#### Absorption

Peak plasma concentrations after 3 hr (oral); 0.9 hr (IM); 3 min (IV).

#### Excretion

Via urine.

### **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.

**Mecobalamin**

The recommended dietary allowances (RDAs) of vitamin B12 are: Infants 0-6 months, 0.4 mcg; infants 7-12 months, 0.5 mcg; children 1-3 years, 0.9 mcg; children 4-8 years, 1.2 mcg; children 9-13 years, 1.8 mcg; older children and adults, 2.4 mcg; pregnant women, 2.6 mcg; and breast-feeding women, 2.8 mcg. Because 10% to 30% of older people do not absorb food-bound vitamin B12 efficiently, those over 50 years should meet the RDA by eating foods fortified with B12 or by taking a vitamin B12 supplement. Supplementation of 25-100 mcg per day has been used to maintain vitamin B12 levels in older people.

**EXPIRY DATE:**

Do not use later than the date of expiry.

**STORAGE:**

Store in a dry & dark place at a temperature not exceeding 30°C.

**PRESENTATION**

HERFEM PLUS is available as Blister pack of 10 tablets

**MARKETED BY:**

TORRENT PHARMACEUTICALS LTD.

Torrent House, Off Ashram Road,

Ahmedabad-380 009, INDIA

**IN/HERFEM PLUS 100,1.1,22.5mg,1500mcg/OCT-19/04/PI**