

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

FESOVIT SPANSULE CAPSULES

1. GENERIC NAME

Sustained-Release Capsules of Ferrous Sulphate with Vitamin B complex

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Spansule capsule contains:

Dried Ferrous Sulphate IP	: 150 mg
<i>(in time release form, equivalent to 46.8 mg of elemental iron)</i>	
Folic Acid IP	: 1 mg
Cyanocobalamin IP	: 15 mcg
Pyridoxine Hydrochloride IP	: 2 mg
Nicotinamide IP	: 50 mg

Colour : Carmoisine.

Appropriate overages included for the vitamins.

Colours: Tartrazine and Titanium dioxide IP in empty capsule shells

3. DOSAGE FORM AND STRENGTH

Sustained-release capsules

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Prevention of iron deficiency anemia in patients with co-existing vitamin B complex deficiency.

4.2 Posology and Method of Administration

FESOVIT should not be sucked, chewed or kept in the mouth, but swallowed whole with a glass of water and should not be taken with hot liquids.

Route of Administration

For oral use.

Adults

One capsule once daily.

Children

FESOVIT is not indicated for paediatric use (see 4.3 Contraindications).

Elderly

There are no relevant data available.

4.3 Contraindications

FESOVIT is contraindicated in:

- Hypersensitivity to any of the *FESOVIT* ingredients,
- Oesophageal stricture, active peptic ulcer, regional enteritis and ulcerative colitis,
- Problems with incorporation of iron (sickle cell anaemia, anaemia associated with lead poisoning, thalassaemia, porphyria cutanea tarda) and forms of anaemia secondary to other haemoglobinopathies,
- Confirmed iron intolerance (e.g. severe inflammatory changes of the gastrointestinal tract),
- Severe hepatic and renal dysfunction,
- Paediatric use,
- Haemolytic anaemia, pernicious anaemia (see 4.4 *Special Warnings and Precautions for use*),
- Patients with inflammatory bowel disease, intestinal strictures and diverticulae,
- Concomitant use with parenteral iron,
- Iron overload (haemosiderosis, haemochromatosis, chronic haemolysis with signs of iron accumulation, sideroblastic anaemia, repeated blood transfusion, concomitant parenteral iron)
- Paroxysmal nocturnal haemoglobinuria,
- Long term folate therapy in any patient with untreated cobalamin deficiency (see 4.4 *Special Warnings and Precautions for use*),
- Malignant disease unless megaloblastic anaemia owing to folate deficiency is an important complication.

4.4 Special Warnings and Precautions for Use

Gastrointestinal Inflammation

Some post-gastrectomy patients show poor absorption of iron.

Stool darkening

Similarly to other oral iron products, consumption of *FESOVIT* may lead to darkening of the stool, giving the appearance of tarry stool.

Teeth darkening and mouth ulcerations

Tooth discoloration may occur during therapy with *FESOVIT*. According to the scientific literature, this tooth discoloration can either regress spontaneously after discontinuation of the medicinal product, or has to be removed by abrasive toothpaste or by professional dental cleaning.

Due to the risk of mouth ulcerations and tooth discolouration, capsules should not be sucked, chewed or kept in the mouth, but swallowed whole with water.

Investigations

Benzidine or similar tests for detection of faecal occult blood may yield false positives. *FESOVIT* must be discontinued for 3 days prior to the planned performance of this test.

Parenteral iron therapy

FESOVIT should not be used together with parenteral iron therapy (see 4.5 *Drug Interactions*).

Elderly

Particularly elderly people presenting with blood or iron loss of unknown origin have to be carefully examined for the source of haemorrhage.

Children

Iron preparation may cause poisoning especially among children. Iron overdose may be fatal (see 4.9 *Overdose*).

Pernicious anaemia or Vitamin B₁₂ deficiency

The folic acid content is unlikely to mask pernicious anaemia should this condition be present; pregnancy during pernicious anaemia is very rare.

Patients with vitamin B₁₂ deficiency should not be treated with folic acid unless administered with adequate amounts of hydroxocobalamin, as it can mask the condition but the subacute irreversible damage to the nervous system will continue. The deficiency can be due to undiagnosed megaloblastic anaemia including in infancy, pernicious anaemia or macrocytic anaemia of unknown etiology or other cause of cobalamin deficiency, including lifelong vegetarians.

Iron aspiration

Aspiration of iron sulphate tablets can cause necrosis of the bronchial mucosa which may result in coughing, haemoptysis, bronchostenosis and/or pulmonary infection (even if aspiration happened days to months before these symptoms occurred). Elderly patients and patients who have difficulties swallowing should only be treated with iron sulphate tablets after a careful evaluation of the individual patient's risk of aspiration. Alternative formulations should be considered. Patients should seek medical attention in case of suspected aspiration.

Megaloblastic anaemias

The dose of folic acid provided is inadequate for the treatment of megaloblastic anaemias. The development of anaemia despite prophylaxis with this medicinal product requires further investigation and appropriate therapy.

Erythropoietic protoporphyria

Iron preparations should be used with caution in patients with erythropoietic protoporphyria

Vision disorders

FESOVIT should not be used for Leber's disease or tobacco amblyopia since these optic neuropathies may degenerate further due to cyanocobalamin (vitamin B₁₂).

Long-term treatment

Long-term use of large doses of pyridoxine (vitamin B₆) is associated with the development of severe peripheral neuropathies; the dose at which these occur is not established.

Treatment preparation and monitoring

FESOVIT should, if possible, not be given to patients with suspected vitamin B₁₂ deficiency without first confirming the diagnosis, as it contains cyanocobalamin.

Other

Failure to respond to treatment may indicate other causes of anaemia and should be further investigated.

Patients suffering from iron overload are particularly susceptible to infection. Treatment of iron overload should be with caution.

In cases of delayed gastric emptying, pyloric stenosis and confirmed intestinal diverticulosis, liquid rather than solid formulations of iron should be administered.

Caution should be exercised when administering folic acid to patients who may have folate dependent tumours.

This product is not intended for healthy pregnant women where lower doses are recommended, but for pregnant women with folic acid deficiency or women at risk for the reoccurrence of neural tube defect.

4.5 Drug Interactions

Intravenous administration of iron salts

Administration of iron intravenously concomitantly with oral administration of iron may induce hypotension or even collapse due to the fast release of iron due to saturation of transferrin. The combination is not recommended.

Antibiotics

Orally administered iron salts inhibit the absorption and the enterohepatic circulation of doxycycline. The combination should be avoided.

The effects of iron and tetracycline products are reduced with their concurrent administration. Tetracyclines form poorly soluble combinations with iron, leading to decreased absorption of

both iron and tetracycline. The interval between the administration of *FESOVIT* and tetracyclines other than doxycycline (see above) should be at least 3 hours.

The response to iron may be delayed in patients receiving systemic chloramphenicol. Chloramphenicol delays plasma clearance of iron and incorporation of iron into red blood cells by interfering with erythropoiesis

When iron salts are co-administered with fluoroquinolones, the absorption of the latter is significantly impaired. The absorption of norfloxacin, levofloxacin, ciprofloxacin, gatifloxacin and ofloxacin is inhibited by iron between 30 and 90%. Fluoroquinolones should be administered at least 2 hours before or at least 4 hours after ferrous-containing medicines.

Antituberculous drugs (such as isoniazid) may increase the requirements for folic acid and pyridoxine (vitamin B₆).

Neomycin used orally may reduce the absorption of vitamin B12 and iron.

Folic acid antagonists

Folate deficiency states may be produced by folic acid antagonists such as methotrexate, pyrimethamine, triamterene, trimethoprim and sulfonamides such as sulfasalazine.

Cholestyramine

Cholestyramine inhibits intestinal absorption of iron.

Penicillamine

FESOVIT decreases the absorption of penicillamine derivatives, therefore doses should be separated by at least 3 hours.

Gold compounds

The absorption gold compounds is decreased by iron products.

Phosphates

Concomitant administration of phosphates may reduce iron absorption. Oral iron preparations should not therefore be taken within 1 hour before or 2 hours after taking such medications.

Salicylates, phenylbutazone and oxyphenbutazone

The concurrent oral administration of *FESOVIT* and salicylates, phenylbutazone or oxyphenbutazone may enhance their irritant effect on the gastric and intestinal mucosa.

Antacids and other calcium compounds

Antacids containing oxides, hydroxides or salts of magnesium, aluminium and calcium, chelate iron salts. The interval between the administrations of these compound groups should therefore

be as long as possible; the minimum time is 2 hours between the administration of the antacid and iron.

Antacids and proton pump inhibitors

Absorption of iron may be reduced in the presence of antacids and proton pump inhibitors which reduce stomach acid.

Iron complexing agents (such as oxalates, phytates, phosphates and magnesium trisilicate, trientine and zinc salts)

Compounds containing calcium and magnesium oxalates, phytates and phosphates (which are contained in vegetable food and constituents of milk, coffee and tea) or carbonates and zinc salts, also impair iron absorption by formation of insoluble complexes. The interval between the administrations of these compounds should be at least 2 hours.

Levodopa, carbidopa, entacapone bisphosphonates, thyroid hormones, mycophenolate, cefdinir and zinc

Iron reduces the absorption of levodopa, carbidopa, entacapone, bisphosphonates, thyroid hormones such as levothyroxine (give at least 2 hours apart), mycophenolate, cefdinir and zinc.

FESOVIT contains vitamin B6 which reduces the effects of levodopa, but this does not occur if a dopa decarboxylase inhibitor is also given.

Methyldopa

The hypotensive effect of methyldopa is reduced by iron.

Bisphosphonates

Iron containing medicinal products form complexes with bisphosphonates *in vitro*. When iron salts are co-administered with bisphosphonates, the absorption of bisphosphonate may be impaired. The time-interval between the administrations of these medicinal products should be at least 2 hours. Iron supplements should not be taken within one hour before or two hours after ingestion of these products.

Thyroid hormones

When co-administered, the absorption of thyroxine is inhibited by iron, which can affect the result of the treatment. The interval between the administrations of the compounds should be at least 2 hours.

Nonsteroidal anti-inflammatory agents

Concomitant administration of iron salts with non-steroidal anti-inflammatory agents may intensify the irritant effect on the gastrointestinal mucosa.

Sulphonamides, anticonvulsants and barbiturates

Sulphonamides, anticonvulsants and barbiturates impair the absorption of folic acid.

There is a specific interaction between phenytoin and folate such that chronic phenytoin use produces folate deficiency. Correction of the folate deficiency reduces plasma phenytoin with potential loss of seizure control. Similar but less marked relationship exist with all anti-convulsant treatments including sodium valproate, carbamazepine and the barbiturates. Sulphasalazine and triamterene also inhibit absorption.

Dimercaprol

The concomitant use of dimercaprol and iron must be avoided.

Mycophenolate mofetil

Oral iron preparations significantly reduce the absorption of mycophenolate mofetil.

Oral contraceptives

Serum concentration of vitamin B₆, vitamin B₁₂ and folic acid may be decreased by use of oral contraceptives.

Hydralazine

Many drugs may increase the requirements for pyridoxine; such drugs include hydralazine.

Antiepileptics/ anticonvulsants

Vitamin B₆ and folic acid has been reported to decrease serum concentrations of phenobarbital and phenytoin.

Serum levels of anticonvulsant drugs may be reduced by the co-administration of folate e.g. folic acid possibly reduces the plasma concentration of phenobarbital, phenytoin and primidone.

Replacement therapy with folinic acid or folic acid may become necessary during antiepileptic therapy in order to prevent megaloblastic anaemia developing.

Altretamine

FESOVIT contains vitamin B₆ which reduces the activity of altretamine.

Alcohol

Alcohol may produce folate deficiency states.

Acetohydroxamic acid

Iron chelates with acetohydroxamic acid reducing the absorption of both.

Dimercaprol

Concomitant use of iron and dimercaprol should be avoided as toxic complexes may form.

Eltrombopag

Iron possibly reduces the absorption of eltrombopag (give at least 4 hours apart).

Raltitrexed

Concomitant use of folic acid with raltitrexed should be avoided.

Calcium, oral magnesium salts and other mineral supplements, zinc and trientine

Iron absorption may be reduced with calcium, oral magnesium salts and other mineral supplements, zinc and trientine. If treatment with both iron and trientine is necessary, a suitable interval is advised.

Food

Administration of iron salts with food may impair the absorption of iron (e.g. tea, coffee, wholegrain cereals, eggs and milk).

The concurrent intake of products with a high content of vegetable constituents, phosphates and tannins limits the absorption of iron, while fish, meat and food with a high content of ascorbic acid and fruit acids have the opposite effect.

Other

Absorption of vitamin B₁₂ from the gastrointestinal tract may be reduced by aminosalicic acid, histamine H₂-antagonists, and colchicine.

Concomitant administration of gastric acid neutralising agents, drugs containing: bicarbonates, carbonates or oxalates, may reduce iron absorption. *FESOVIT* should not therefore be taken within 1 hour before or 2 hours after taking the above medications.

Antibacterials, and co-trimoxazole, may interfere with folate metabolism. Folate supplements enhance the efficacy of lithium therapy. Methotrexate and trimethoprim are specific anti-folates and the folate deficiency caused by their prolonged use cannot be treated by folic acid containing tablets. Folinic acid should be used. Nitrous oxide anaesthesia may cause an acute folic acid deficiency. Both ethanol and aspirin increase folic elimination.

4.6 Use in Special Population

Pregnancy and Lactation

During pregnancy and lactation, use of *FESOVIT* should always be under the direction of a physician.

Use of any drug during the first trimester of pregnancy should be avoided if possible. Thus, administration of iron during the first trimester however requires evidence of iron deficiency. Prophylaxis of iron deficiency during the remainder of pregnancy is justified.

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. Lack of the vitamin or its metabolites may also be responsible for some cases of spontaneous abortion and intrauterine growth retardation.

Folic acid is excreted in 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. The amount of iron and folic acid, which is transferred from *FESOVIT* to breast milk has not been determined and it is not known if adverse events may occur in the breastfed children of mothers who receive this form of treatment.

4.7 Effects on Ability to Drive and Use Machines

There are no clinical data proving that *FESOVIT* may have an influence on the ability to drive or use machines.

4.8 Undesirable Effects

As *FESOVIT* contains iron, it may sometimes produce gastrointestinal irritation and abdominal pain with nausea and vomiting.

Adverse effects can be reduced by giving it with or after food (rather than on an empty stomach).

The following adverse events have been reported for the ingredients of *FESOVIT*. Frequency of these events cannot be estimated from the available data.

Gastrointestinal disorders

Faeces discoloured, abdominal bloating, abdominal pain upper, constipation (particularly in older patients which may lead to faecal impaction), diarrhoea, nausea, flatulence, vomiting, tooth discolouration (see 4.4 *Special Warnings and Precautions for Use*), heartburn, abdominal pain, anorexia, gastrointestinal irritation, mouth ulceration*

** in the context of incorrect administration, when the capsules are chewed, sucked or kept in mouth. Elderly patients and patients with deglutition disorders may also be at risk of oesophageal lesions or of bronchial necrosis, in case of false route.*

Skin and subcutaneous tissue disorders

Dermatitis allergic, hypersensitivity reactions of the skin, e.g. exanthema, rash (sometimes severe), dyspnoea, urticaria photosensitivity, pruritus and shock.

General

Headache and dizziness

Metabolism and nutrition disorders

Haemosiderosis may occur as a result of excessive or mistaken therapy

Immune system disorders

Hypersensitivity reactions, anaphylactic reaction including anaphylaxis (see *Skin and subcutaneous tissue disorders*)

Respiratory, thoracic and mediastinal disorders

Bronchostenosis (see 4.4 *Special Warnings and Precautions for use*)

Other

Sensory neuropathy, diabetogenic effects.

4.9 Overdose

Iron overdosage is an acute emergency requiring urgent medical attention. An acute intake of 75mg/kg of elemental iron is considered extremely dangerous in young children.

Signs and Symptoms

Symptoms of intoxication may include restlessness, stomachache, nausea, vomiting and diarrhea, the faeces show a tarry coloration, the vomit can contain blood, shock, convulsions, metabolic acidosis and coma, a phase of apparent recovery that may last up to 24 hours, shock and acidosis. Death can occur after convulsions, Cheyne-Stokes breathing, coma and pulmonary oedema. Delayed effects of acute poisoning may appear from 2 to 6 weeks after overdose with intestinal obstruction, pyloric stenosis and extensive scarring of the gastric mucosa. Precipitation or exacerbation of the neurological damage of vitamin B12 deficiency, severe peripheral neuropathies, sensory neuropathy, abdominal pain, loss of appetite, breast soreness, photosensitivity, headache and dizziness, elevation in liver tests and liver damage, including jaundice and parenchymal liver cell injury.

Treatment

The ingestion of raw eggs and milk results in the formation of compounds with ferrous ions and therefore this decreases absorption.

In severe cases of poisoning, particularly if the serum iron concentration exceeds the total iron binding capacity, desferrioxamine, an iron chelating agent, should be administered orally or parenterally as a specific antidote. Severe acute poisoning in infants should always be treated with desferrioxamine at a dose of 90 mg/kg im followed by 15 mg/kg per hour I.V.

Dimercaprol is contraindicated because of the formation of toxic compounds.

Treatment also includes monitoring of the status of the circulation through standard examination and the observation of other signs, particularly fluid balance and acid-base imbalance.

Chronic overdose

Chronic overdose may present as haemosiderosis or haemochromatosis. This is especially likely if anaemia resistant to treatment is erroneously diagnosed as iron deficiency.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action and Pharmacodynamic effects

Iron

Iron provided by *FESOVIT* aids haemoglobin regeneration. 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.

Folic acid

Folic acid, after conversion in the body to folinic acid, takes part in reactions involved in the synthesis of nucleotides and maturation of RBCs in conjunction with vitamin B12. It also plays an important role in lymphocyte-mediated immune response.

Vitamin B₁₂ (cyanocobalamin)

It is essential for erythropoiesis, formation of myelin sheath and synthesis of the DNA.

Vitamin B₆ (pyridoxine hydrochloride)

It takes part in formation of some important co-enzymes involved in protein metabolism and HEM biosynthesis. As a coenzyme it functions in metabolism of amino acids, glycogen and sphingoid bases.

Nicotinamide

Nicotinamide has a role in reduction of blood cholesterol and triglycerides. It is essential for the synthesis of hormones such as estrogens, progesterone, cortisone, thyroxin and insulin.

5.2 Pharmacokinetic Properties

FESOVIT capsule containing iron, folic acid and B complex is developed in a 'timed release' oral preparation called the sustained release capsule.

Iron

Each sustained release capsule contains hundreds of tiny pellets, and each pellet has a core of sugar or starch, to which the active drug is applied. In a sustained release capsule, there are several sets of pellets, each set coated with differing thickness of semi-permeable wax. The special coating ensures that little or no iron is released in the easily irritated stomach. As each pellet passes through the alimentary tract, fluid begins to pass gradually through the coating and is absorbed. The medicated core swells and eventually ruptures the coating, releasing the active drug. As each batch of pellets successively ruptures, the active ingredient is gradually and constantly released on its way through the GI tract. The sustained release mechanism thus

ensures that iron is made available in small quantities over a period of time in the sites of maximal absorption in the duodenum and jejunum. The high bioavailability of iron in the sustained release capsule indicates that less iron needs to be administered to the patient for a given haematopoietic response.

There are no relevant data available for the other ingredients.

6. NONCLINICAL PROPERTIES

There are no relevant data available.

7. DESCRIPTION

Sustained-release capsules

Each Spansule capsule contains:

Dried Ferrous Sulphate IP	: 150 mg
<i>(in time release form, equivalent to 46.8 mg of elemental iron)</i>	
Folic Acid IP	: 1 mg
Cyanocobalamin IP	: 15 mcg
Pyridoxine Hydrochloride IP	: 2 mg
Nicotinamide IP	: 50 mg

Colour : Carmoisine.

Appropriate overages included for the vitamins.

Colours: Tartrazine and Titanium dioxide IP in empty capsule shells

8. PHARMACEUTICAL PARTICULARS

List of Excipients

Non-Pareil seeds containing:

Sucrose, Starch, Polyvinyl Pyrrolidone and Talc.

Iron waxed pellets containing:

Bees wax white, Methylene chloride, Isopropyl alcohol and Glyceryl monostearate

Hard gelatin Capsule Shells containing:

Gelatin, Methyl paraben, Propyl paraben, Purified water, SLS, Tartrazine and Titanium dioxide.

8.1 Incompatibilities

There are no relevant data available.

8.2 Shelf Life

The expiry date is indicated on the label and packaging.

8.3 Packaging Information

Blister strips of capsules in a carton.

8.4 Storage and Handling Information

Store at a temperature not exceeding 30° C.

Keep out of reach of children.

There are no special requirements for use or handling of this product.

9. PATIENT COUNSELLING INFORMATION

Registered Medical Practitioners may counsel their patients about the special warnings and precautions for use, drug interactions, undesirable effects, and any relevant contra-indications of *FESOVIT*. Patients may also be informed about posology, method of administration and storage/handling information as applicable.

10. DETAILS OF MANUFACTURER

The Manufacturing Site details are mentioned on the label and packaging.

For further information please contact:

GlaxoSmithKline Pharmaceuticals Limited.

Registered Office

Dr. Annie Besant Road, Worli
Mumbai 400 030, India.

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Manufacturing License number is indicated on the label and packaging.

12. DATE OF REVISION

05-MAY-2020

Trade marks are owned by or licensed to the GSK group of companies

Version: FST/PIIN/2020/01

Adapted from:

- *Ferrous Sulphate/Folic Acid NCDS version 05 dated 17-Sep-2019.*
- *Theragran H NCDS version-04 dated 23-November-2018.*
- *PDR for Nutritional Supplements - 2nd Edition.*