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

FEFOL-Z CAPSULES

1. GENERIC NAME

Capsules of Carbonyl Iron with Zinc Sulphate Monohydrate and Folic Acid

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains:

Carbonyl Iron 50 mg equivalent to Elemental Iron 50 mg
Zinc Sulphate Monohydrate IP 61.8 mg (equivalent to 22.5 mg of elemental Zinc)
Folic Acid IP 0.5 mg (Appropriate overages included for Folic Acid)
Approved colours used in empty gelatin capsule shell.

List of Excipients

Non-Pareil seeds, Hard gelatin Capsules.

3. DOSAGE FORM AND STRENGTH

Oral Capsules

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication

FEFOL-Z CAPSULES is indicated for prophylaxis of iron, folic acid and zinc deficiency:

- during pregnancy and lactation.
- in individuals following a restrictive diet which may be deficient in iron, zinc and folic acid.

4.2 Posology and Method of Administration

FEFOL-Z CAPSULES 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.

The capsule is to be taken at sufficient intervals from meals (for instance, on an empty stomach in the morning or between two principal meals), because absorption can be reduced by ingredients of food.

Route of Administration

For oral use.

Adults

One capsule daily.

Children

Contraindicated in paediatric use (see *4.3 Contraindications).*

Elderly

There are no relevant data available.

Renal impairment

Contraindicated in severe renal dysfunction (see *4.3 Contraindications).*

Hepatic impairment

Contraindicated in severe hepatic dysfunction (see *4.3 Contraindications).*

4.3 Contraindications

FEFOL-Z CAPSULES is contraindicated in the following conditions:

- hypersensitivity to any of the product ingredients.
- oesophageal stricture, active peptic ulcer, regional enteritis and ulcerative colitis.
- iron overload (haemosiderosis, haemochromatosis, chronic haemolysis with signs of iron accumulation, sideroblastic anaemia, repeated blood transfusion, concomitant parenteral iron).
- 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.
- 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.
- copper deficiency (see *4.5 Drug Interactions*)

4.4 Special Warnings and Precautions for Use

Gastrointestinal inflammation

Some post-gastrectomy patients show poor absorption of iron.
Care should be taken when administering oral iron products to patients with active gastrointestinal inflammation (such as gastritis, history of peptic ulcer).

Stool darkening

Similarly, to other oral iron products, consumption 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 iron-containing drugs.
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. Product must be discontinued for 3 days prior to the planned performance of this test.

Parenteral therapy

Oral and parenteral iron therapy should not be used together *(*see *4.5 Drug Interaction).*

Elderly

Particularly elderly people presenting with blood or iron loss of unknown origin have to be carefully examined for the cause of anaemia/ 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 B_{12} 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 B_{12} 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 aetiology or other cause of cobalamin deficiency, including lifelong vegetarians.

Iron aspiration

Aspiration of iron containing tablets/capsule 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 containing tablets/capsules 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.

Other

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.

Accumulation of zinc may occur in cases of renal failure.

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.

Oral Iron

The absorption of zinc may be reduced by oral iron, also the absorption of oral iron may be reduced by zinc.

Doxycycline

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

Tetracyclines

The effect of iron and tetracycline products is reduced with their concurrent administration. Tetracyclines form poorly soluble combinations with iron, leading to decreased absorption of both iron and tetracycline. Zinc may reduce the absorption of concurrently administered tetracyclines, also the absorption of zinc may be reduced by tetracyclines. The interval between the administration of *FEFOL-Z CAPSULES* and tetracyclines other than doxycycline should be at least 3 hours.

Cholestyramine

Cholestyramine inhibits intestinal absorption of iron.

Penicillamine, gold compounds and dietary phosphates

The absorption of penicillamine, gold compounds and dietary phosphates is decreased during treatment with iron products. The absorption of zinc may be reduced by penicillamine, also the absorption of penicillamine may be reduced by zinc.
Penicillamine should be administered at least 2 hours before *FEFOL-Z CAPSULES*.

Salicylates, phenylbutazone and oxyphenbutazone

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

Chloramfenicol

The concomitant administration of chloramphenicol may delay the therapeutic action of iron and its compounds.

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.

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 and methyldopa

Iron salts can also decrease absorption of other drugs including levodopa, carbidopa and methyldopa.

The interval between the administrations of these compounds should be as long as possible.

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.

Fluoroquinolones

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 iron containing medicines.
Zinc may reduce the absorption of quinolones; ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin and ofloxacin.

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.

Other

Administration of iron salts with food may impair the absorption of iron.

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.

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.

Copper

Zinc may inhibit the absorption of copper (see *4.3 Contraindications*)

Calcium Salts

The absorption of zinc may be reduced by calcium salts.

Trientine

The absorption of zinc may be reduced by trientine, also the absorption of trientine may be reduced by zinc.

4.6 Use in Special Populations

Fertility

There is no relevant data available.

Pregnancy

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.

FEFOL-Z CAPSULES are administered when prescribed by a doctor. 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. Lack of the vitamin or its metabolites may also be responsible for some cases of spontaneous abortion and intrauterine growth retardation.

Lactation

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 *FEFOL-Z CAPSULES* 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.

Zinc crosses the placenta and is present in breast milk.

FEFOL-Z CAPSULES is administered when prescribed by a doctor.

4.7 Effects on Ability to Drive and Use Machines

No effects on the ability to drive and use machines have been observed

4.8 Undesirable Effects

Post Marketing Data

Adverse drug reactions (ADRs) are listed below by MedDRA system organ class and by frequency.

Frequencies are defined as:

Very common ≥1/10
Common ≥1/100 to <1/10
Uncommon ≥1/1000 to <1/100
Rare ≥1/10000 to <1/1000
Very rare <1/10000
Not known (cannot be estimated from the available data).

Gastrointestinal disorders

Common: faeces discoloured *(*see *4.4 Special Warnings and Precautions for Use).*

Uncommon: abdominal bloating, abdominal pain upper, constipation (particularly in older patients which may lead to faecal impaction), diarrhoea, nausea.

Rare: Flatulence

Not known: 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.

Immune system disorders

Not known: 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*)

Skin and subcutaneous tissue disorders

Very rare: dermatitis allergic

Not known: hypersensitivity reactions of the skin, e.g. exanthema, rash (sometimes severe), pruritus, dyspnoea, shock and urticaria

Zinc salts may cause abdominal pain, dyspepsia, nausea, vomiting, diarrhoea, gastric irritation and gastritis. There have also been cases of irritability, headache and lethargy observed.

Zinc may interfere with the absorption of copper, leading to reduced copper levels, and potentially copper deficiency. The risk of copper deficiency may be greater with long-term treatment (e.g. if zinc deficiency is no longer present) and/or with higher doses of zinc. Signs of copper deficiency can include neurological symptoms e.g. polyneuropathy (symptoms of which can include gait disturbances, ataxia and paraesthesia and/or hypoaesthesia) and haematological symptoms e.g. anaemia, neutropenia, leucopenia and pancytopenia.

4.9 Overdose

Iron Overdose

Symptoms of intoxication may appear after dosages as small as 20 mg of Fe^{2+} /kg body weight (BW). The appearance of serious toxic effects must be anticipated for dosages from 60 mg of Fe^{2+}/ kg BW and more. Intoxications by dosages of 200 to 400 mg of Fe^{2+} /kg BW result in death when left untreated.

Overdosage of iron is particularly dangerous to young children. A dose as small as 400 mg of Fe^{2+} can lead to life-threatening states in infants.

Symptoms and signs

Iron poisoning can show several phases.

- During the first phase, about 30 minutes to 5 hours following oral administration, symptoms such as restlessness, stomachache, nausea, vomiting and diarrhoea are observed. The faeces show a tarry coloration, the vomit can contain blood. Shock, convulsions, metabolic acidosis and coma can develop
- This is often followed by a phase of apparent recovery that may last up to 24 hours
- Then diarrhoea, shock and acidosis reappear. 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. The dose of folic acid contained in the product excludes any risk of folic acid overdose.

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.

Further management should be as clinically indicated.

Zinc Sulphate Overdose

Zinc sulfate is corrosive in overdosage.

Symptoms and signs

Corrosion and inflammation of the mucous membrane of the mouth and stomach; ulceration of the stomach followed by perforation may occur.

Treatment

Gastric lavage and emesis should be avoided. Demulcents such as milk should be given. Chelating agents such as sodium calcium edetate may be useful.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action and Pharmacodynamic Effects

Iron aids haemoglobin regeneration.

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 B_{12}. It also plays an important role in lymphocyte-mediated immune response.

Zinc is an essential trace element involved in many enzyme systems.

5.2 Pharmacokinetic Properties

Carbonyl iron

When iron is taken orally, the acidic environment of the stomach maintains iron in its more soluble ferrous (and more readily absorbed) state. Iron is then absorbed through the duodenum

and upper small intestines. Although orally administered iron is absorbed in the duodenum, iron directly instilled into the duodenum is poorly absorbed. Intraduodenal pH is much higher than intragastric pH due to the high concentration of pancreatic secretions in the duodenum. Both ascorbic acid and meat (heme iron) will increase the absorption of non-heme iron. A hematopoietic transcription factor, known as NF-E_2, regulates the absorption of iron by the oral route in response to erythropoiesis. Increased oral uptake into the systemic circulation occurs when iron deficiency or increased erythropoiesis (e.g., epoetin alfa therapy) is present. When iron stores are adequate, less iron is absorbed across the intestinal mucosa. The absorptive process across the intestine is finite, limiting the amount of entry of iron into the systemic circulation on a daily basis, even in deficiency. Oral iron absorption rarely exceeds 2 mg/day.

Folic acid

Following oral administration, folic acid is rapidly absorbed from the small intestine. Because dietary folate is primarily in the polyglutamyl form, it must be converted to the monoglutamate form by intestinal conjugase enzymes prior to absorption. The monoglutamate form is then reduced and methylated to methyltetrahydrofolate by dihydrofolate reductase during transport across the intestinal mucosa.

Zinc

Zinc is absorbed from the gastrointestinal tract and distributed throughout the body. The highest concentrations occur in hair, eyes, male reproductive organs and bone. Lower levels are present in liver, kidney and muscle. In blood 80% is found in erythrocytes. Plasma zinc levels range from 70 to 110µg/dL and about 50% of this is loosely bound to albumin. About 7% is amino-acid bound and the rest is tightly bound to alpha 2-macroglobulins and other proteins.

6. NONCLINICAL PROPERTIES

There are no relevant data available.

7. DESCRIPTION

Each capsule contains:

Carbonyl Iron 50 mg equivalent to Elemental Iron 50 mg
Zinc Sulphate Monohydrate IP 61.8 mg (equivalent to 22.5 mg of elemental Zinc)
Folic Acid IP 0.5 mg
(Appropriate overages included for Folic Acid)
Approved colours used in empty gelatin capsule shell.

List of Excipients

Non-Pareil seeds, Hard gelatin Capsules.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

There are no relevant data available.

8.2 Shelf Life

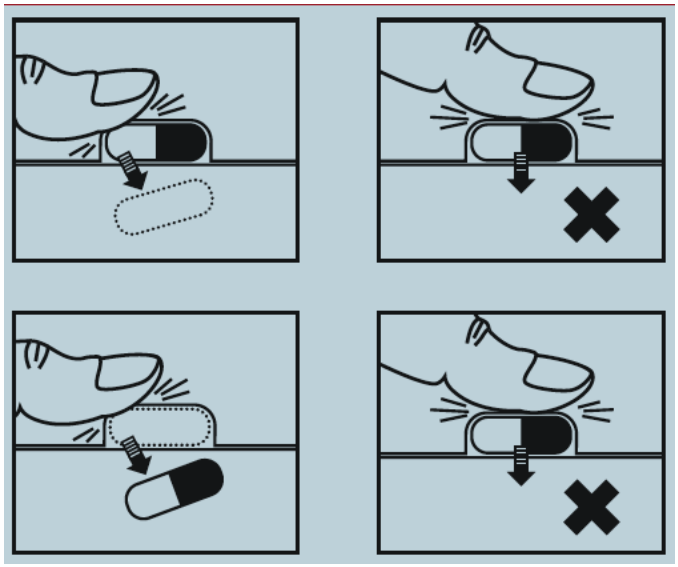
The expiry date is indicated on the label and packaging.

8.3 Packaging Information

Strips of capsules in a carton.

Child Resistant Packaging

These capsules come in special packaging to prevent children removing them. To take out a capsule and avoid possible damage gently push one end of the capsule through the foil layer. Do not push in the middle of the capsule.



8.4 Storage and Handling Instructions

Store in a dry place at temperature not exceeding 30^{o} C.
Keep out of reach of children.
For oral use only.

9. PATIENT COUNSELLING INFORMATION

Registered Medical Practitioners may counsel their patients (and/or patients' caregiver as applicable) about the special warnings and precautions for use, drug interactions, undesirable effects, and any relevant contra-indications of *FEFOL-Z CAPSULES*. Patients (and/or patients' caregiver) 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

22-JAN-2024

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

Version No: FEFZ/PI/IN/2024/01

Adapted from:

1. *Ferrous Sulphate + Folic Acid (Fefol Spansule) NCDS version 05 dated 17 September 2019.*
2. *Solvazinc 45mg Effervescent Tablets SmPC (last updated on emc: 18 Oct 2023). Available from: https://www.medicines.org.uk/emc/product/4930/smpc*