IBERET® FOLIC 500

PRODUCT NAME
Iberet® Folic 500 (Controlled-Release Iron with Vitamin C and Vitamin B-Complex Including Folic Acid) Filmtab

PRODUCT DESCRIPTION

Iberet® Folic 500 Film-Coated Tablet is a smooth, filmseal coating tablet, oblong and elongated shape, red in colour and with characteristic odour.

Iberet® Folic 500 Filmtab tablets contain 525 mg of ferrous sulfate (equivalent to 105 mg of elemental iron) in a unique controlled-release vehicle, the Gradumet. In addition, this product contains ascorbic acid present as sodium ascorbate and the B-Complex vitamins including folic acid.

Each Filmtab tablet provides:

Ferrous Sulfate (equivalent to 105mg of elemental Iron)	525 mg
Vitamin C	500 mg
Niacinamide	30 mg
Calcium Pantothenate	10 mg
Vitamin B1 (Thiamine mononitrate)	6 mg
Vitamin B2 (Riboflavin)	6 mg
Vitamin B6 (Pyridoxine hydrochloride)	5 mg
Vitamin B12 (Cyanocobalamin)	25 mcg
Folic Acid	800 mcg

Inactive Ingredients
Cellulosic polymers, corn starch, FD&C Red No. 7, FD&C Blue No. 1, FD&C Blue No. 2, FD&C Red No. 3, magnesium stearate, methyl acrylate-methyl methacrylate copolymer, polyethylene glycol, povidone, propylene glycol, stearic acid, talc, titanium dioxide, vanillin and other ingredients.

The Gradumet is an inert, porous, plastic matrix which is impregnated with ferrous sulfate. Iron is leached from the Gradumet as it passes through the gastrointestinal tract, and the expended matrix is excreted harmlessly in the stool. Controlled-release iron is particularly helpful in patients who have demonstrated intolerance to oral iron preparations.

INDICATIONS AND USAGE

Iberet® Folic 500 is indicated in non-pregnant adults for the treatment of iron deficiency anemia and prevention of concomitant folic acid deficiency where there is an associated deficient intake or increased need for the B-complex vitamins.

Iberet® Folic 500 is also indicated in pregnancy for the prevention and treatment of iron deficiency anemia where there is a concomitant deficient intake or increased need for the B-complex vitamins (including folic acid).

DOSAGE AND ADMINISTRATION

Iberet® Folic 500 is administered orally and may be taken on an empty stomach. Adults and pregnant women who require treatment for iron and folic acid deficiency, the recommended dose is one tablet daily or according to the doctor's directions.

Do not chew or crush tablet, swallow whole.

CONTRAINDICATIONS

Iberet® Folic 500 is contraindicated in individuals known to be hypersensitive to any of its components.

Iberet® Folic 500 is contraindicated in patients with thalassemia, sideroblastic anemia, hemochromatosis, and hemosiderosis.

This product should not be used in pediatric patients.

Iberet® Folic 500 is also contraindicated in the rare instance of hypersensitivity to folic acid.

WARNINGS AND PRECAUTIONS

General

Patients should be advised to keep these products out of the reach of children.

Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under six years of age. Keep this product out of the reach of children. In cases of accidental overdose, call a doctor or seek medical advice immediately.

Iron therapy could induce relapse of erythropoietic protoporphyria. Iron overload has been suggested as being involved in the pathogenesis of porphyria cutanea tarda.

Folic acid alone is improper therapy in the treatment of pernicious anemia and other megaloblastic anemias where vitamin B_{12} is deficient.

Where anemia exists, its nature should be established and underlying causes determined.

Iberet® Folic 500 contains increased amounts (see above) of folic acid per tablet. Folic acid especially in doses above 0.1 mg daily may obscure pernicious anemia, in that hematologic remission may occur while neurological manifestations remain progressive. Concomitant parenteral therapy with vitamin B_{12} may be necessary in patients with deficiency of vitamin B_{12}. Pernicious anemia is rare in women of childbearing age, and the likelihood of its occurrence along with pregnancy is reduced by the impairment of fertility associated with vitamin B_{12} deficiency.

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

Caution should be exercised when dosing ascorbic acid in patients with chronic renal failure and in patients receiving acetylsalicylic acid.

Like other oral iron preparations, Iberet® Folic 500 should be stored out of the reach of children to guard against accidental iron poisoning (see **OVERDOSAGE**).

Laboratory Tests

In older patients and those with conditions tending to lead to vitamin B_{12} depletion, serum B_{12} levels should be regularly assessed during treatment with Iberet® Folic 500.

False occult blood tests are possible.

DRUG INTERACTIONS

Absorption of iron is inhibited by magnesium trisilicate, antacids or cholestyramine.

With concomitant use of alcohol, toxic delirium and lactic acidosis have been noted.

Ferrous sulfate may interfere with the absorption of tetracyclines. Therefore, these drugs should be given two to three hours apart.

Concomitant use of niacin and nicotine has been reported to cause increased flushing and dizziness.

Since pyridoxine is noted to have effects on dopamine, drug interactions are possible. A drug interaction with levodopa is noted, but can be avoided if levodopa is given in combination with a decarboxylase inhibitor.

Prothrombin times are decreased when ascorbic acid is used concomitantly with anticoagulants.

Concurrent administration of oral iron preparations may interfere with the oral absorption of some quinolone anti-infective agents (e.g. ciprofloxacin, norfloxacin, ofloxacin) resulting in decreased serum and urine concentrations of the quinolones. Therefore, oral iron preparations should not be ingested with or within two hours of a dose of an oral quinolone.

Drug Food Interactions

Eggs inhibit iron absorption. Coffee and tea consumed with a meal or one hour after a meal may significantly inhibit the absorption of dietary iron. Its clinical significance has not been determined. Oral iron preparations should not be taken within one hour or two hours after ingestion of the above mentioned food products.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Adequate data are not available on long-term potential for carcinogenesis in animals or humans.

PREGNANCY AND LACTATION

Pregnancy
Studies in pregnant women have not shown that Iberet® Folic 500 increases the risk of fetal abnormalities if administered during pregnancy. If this drug is used during pregnancy, the possibility of fetal harm appears remote. Because studies cannot rule out the possibility of harm, however, Iberet® Folic 500 should be used during pregnancy only if clearly needed.

Lactation

Iron and Folic acid are excreted in breast milk. Iberet® Folic 500 can be used during breast-feeding. Avoid excessive doses.

ADVERSE REACTIONS

The likelihood of gastric intolerance to iron in the controlled-release Gradumet vehicle is remote. If such should occur, the tablet may be taken after a meal. Allergic sensitization has been reported following both oral and parenteral administration of folic acid.

Allergic reactions, including rash, pruritus, and anaphylaxis have been reported with vitamin use.

Components of products have been associated with gastrointestinal effects such as heartburn, eructation, abdominal pain and cramps, diarrhea, vomiting nausea, and anorexia.

Hepatic dysfunction with abnormal liver function tests, including hyperbilirubinemia has been noted.

Deterioration of acneform vulgaris, or eruption of acneform exanthema, has been noted with several components.

Bright yellow urine discoloration has been reported with riboflavin usage.

Niacinamide has strong vasodilator effects, most often characterized by flushing, dizziness or faintness.

Peripheral sensory neuropathies have been noted with usage of pyridoxine.

Stone formation, crystalluria, and oxalosis, with ascorbic acid usage, have been reported in the literature.

Black discoloration of the stool has been reported with iron usage.

Injury to mouth and pharynx, mouth ulceration, esophageal ulcer, hematemesis and ileus have been reported.

Mouth ulceration may occur in case of incorrect use, when the tablets 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.

OVERDOSAGE

Acute overdosage of iron may cause nausea and vomiting and, in severe cases, hepatic necrosis, cardiovascular collapse, and death. The lethal dose of orally ingested elemental iron is estimated to be 180 to 300 mg/kg of body weight. However, a dose of elemental iron as low as 30 mg/kg may be toxic in some individuals and ingestion of doses as low as 60 mg/kg have resulted in death.

Toxicity that occurs with an acute iron overdosage results from a combination of the corrosive effects on the gastrointestinal mucosa and the metabolic and hemodynamic effects caused by the presence of excessive elemental iron.

The signs and symptoms of acute iron poisoning may occur within 10 to 60 minutes or be delayed for several hours. Initial clinical manifestations may encompass acute gastrointestinal irritation, including epigastric pain, nausea, vomiting, diarrhea of green and subsequently tarry stools, melena and hematemesis which may be associated with drowsiness, pallor, cyanosis, lassitude, seizures, shock, and coma. Hepatic necrosis and hepatic failure may develop. Because of potential toxic effects of overdosage, immediate medical attention is warranted.

Iron poisoning should be treated by emptying the stomach via ipecac-induced vomiting or preferably, by gastric lavage with a large bore tube. If the patient has experienced multiple episodes of vomiting, especially if the vomitus contains blood, ipecac syrup should not be administered.

Vomitus should be examined for returned Gradumet tablets. If sufficient tablets are not returned, the possibility of whole gut lavage with 0.9% sodium chloride solution plus a saline cathartic should be considered. Surgical removal of iron tablets, which are visible in abdominal radiographs, may be required if other means of removing the drug are unsuccessful.

The best method for assessing the severity of an iron ingestion is to measure the serum iron and the total iron binding capacity (TIBC). If the serum iron level is greater than TIBC, the potential for systemic toxicity exists. Serum iron and total iron-binding capacity levels may be used as guidelines for use of deferoxamine, an agent used to chelate elemental iron.

Chelation therapy with deferoxamine should be considered when the following conditions exist:

1. a potentially lethal dose (180 to 300 mg/kg or more) of elemental iron has been ingested;
2. serum iron concentrations are greater than 400 to 500 µg/dL.
3. serum iron concentration exceed total iron binding capacity; and/or
4. patients have severe symptoms of iron intoxication such as coma, shock, or seizure.

Hemodialysis is of little value in the treatment of iron intoxication.

Supportive treatment, including suction and maintenance of airway; correction of acidosis and control of shock and dehydration with intravenous fluids or blood, oxygen and vasopressors, should be administered as required.

High doses of individual components of the product have been associated with eczematous and exanthematous skin lesions, fatigue, and insomnia.

In higher niacinamide doses, liver damage, gout and ulcer formation have been noted.

Vasodilatory effects such as giddiness, faintness, vasovagal attacks, and anaphylactic shock have also been reported.

In high doses of pyridoxine, peripheral sensory neuropathy and vesicular skin lesions have been reported.

Hemolysis has been reported at high doses of ascorbic acid, especially in patients with glucose 6 phosphate dehydrogenase deficiency.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Iron, an essential mineral, is a component of hemoglobin, myoglobin and a number of enzymes. The total body content of iron is approximately 50 mg/kg in man and 35 mg/kg in women.

Iron is primarily stored in the body as hemosiderin or ferritin, found in the reticuloendothelialcells of the liver, spleen, and bone marrow. Approximately two-thirds of total body iron is in thecirculatory red blood cell mass in hemoglobin, the major factor in oxygen transport. Concentration of plasma iron and the total iron-binding capacity of plasma vary greatly in different physiological conditions and disease states.

Approximately two-thirds of folic acid is bound to plasma proteins. Half of the folic acid stored in the body is found in the liver. Folic acid is also concentrated in spinal fluid.

Pharmacokinetics

Absorption

The absorption is increased when iron stores are depleted or red blood cell production is increased. Conversely, high iron blood concentrations decrease absorption. The average dietary intake of iron is 18 to 20 mg/day. Approximately 10% of this iron is absorbed in healthy individuals and about 20% to 30% in iron-deficient individuals.

Folic acid and iron are absorbed in the proximal small intestine, particularly the duodenum. Folic acid is absorbed maximally and rapidly at this site, and iron is absorbed in a descending gradient from the duodenum distally. After absorption, folic acid is rapidly converted into its metabolically active forms. Except for the folates ingested in liver, yeast, and egg yolk, the percentage of absorption of food folates averages about 10%.

The ferrous salt form is absorbed three times more readily than the ferric form. The common ferrous salts (sulfate, gluconate, fumarate) are absorbed almost on a milligramfor-milligram basis, but differ in the content of elemental iron. Ferrous sulfate comprises 20% of elemental iron content.

Oral iron is absorbed most efficiently when it is administered between meals. However, conventional iron preparations frequently cause gastric irritation when taken on an empty stomach. Although food can decrease the absorption of iron by 40% to 66%; gastric intolerance may necessitate administering the drug with food.

Studies with iron in the Gradumet have indicated that relatively little iron is released in the stomach, gastric intolerance is seldom encountered, and hematologic response ranks with that obtained from plain ferrous sulfate. Therefore, potential gastric irritation is minimized when iron is administered in the Gradumet form in comparison with conventional oral iron preparations.

Large amounts of ascorbic acid administered orally with ferrous sulfate have been shown to enhance iron absorption. This is apparently due to the ability of ascorbic acid to prevent the oxidation of ferrous iron to the less effectively absorbed ferric form.

The B-Complex vitamins are absorbed by an active transport process; they are rapidly eliminated and therefore are not stored in the body.

Calcium pantothenate is absorbed readily from the gastrointestinal tract and distributed to all body tissues.

Distribution

Ferrous iron passes through gastrointestinal mucosal cells directly into the blood and is immediately bound to transferrin. Transferrin, a glycoprotein $_{B\,1}$-globulin, transports iron to the bone marrow where it is incorporated into the hemoglobin.

Small excesses of iron within the villous epithelial cells are oxidized to the ferric state. Ferric iron combines with the protein apoferritin to yield ferritin and is stored in mucosal cells which are exfoliated at the end of their life span and excreted in the feces.

Elimination

Iron metabolism occurs in a virtually closed system. The majority of iron liberated by destruction of hemoglobin is conserved and reused by the body. The daily excretion of iron from urine, sweat and sloughing of intestinal mucosal cells amounts to approximately 0.5 to 1 mg in healthy men and 1 to 2 mg in menstruating women. The half-life of ferrous sulfate is approximately six hours.

HOW SUPPLIED
Iberet® Folic 500 is supplied as red film-tab.

PRESENTATION
Box of 8’s film-coated tablet
Box of 30’s film-coated tablet
Box of 300’s film-coated tablet

STORAGE
Store at room temperature not exceed 30°C

Manufactured by
PT. Abbott Indonesia
Jl. Raya Jakarta Bogor Km. 37
Depok 16415
Indonesia

Product Registration Holder & Importer
Abbott Laboratories (M) Sdn. Bhd.
27-02, Level 27, Imazium,
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