SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Ferrous fumarate/folic acid/cyanocobalamin 100mg/0.5mg/5mcg per 5 mL oral suspension
Vitcofol

2. Qualitative and quantitative composition

Each 5 mL (approximately teaspoon) contains 100 mg of ferrous fumarate, 0.5 mg of folic acid and 5 mcg of cyanocobalamin (Vitamin B12).

Excipient with known effect
Each 5mL also contains 1.5 mL of sorbitol, 2.5 mg of sucralose and 1.75 mg of carmoisine (see section 4.4).

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Oral suspension.

Red to brown-coloured, orange-flavoured uniform suspension having a sweet taste.

4. Clinical particulars

4.1 Therapeutic indications

Ferrous fumarate/folic acid/cyanocobalamin is indicated for the prophylaxis and treatment of iron deficiency anaemia, folate deficiency and cyanocobalamin (Vitamin B12) deficiency.

4.2 Posology and method of administration

Iron deficiency anaemia
Elemental iron content of ferrous fumarate is 33% and 100 mg ferrous fumarate BP equivalent to 32.79 mg elemental iron.

Adults

- Treatment dose
  100-200 mg daily of elemental iron (8-15 ml of Vitcofol twice daily) or as directed by the physician.
- Prophylactic dose
  60-120 mg daily of elemental iron (10-19 ml of Vitcofol syrup daily).
- Prophylactic dose in pregnancy
  Doses of 40 to 100 mg daily of elemental iron (6-15 ml of Vitcofol syrup daily).

Children

- Treatment dose
  3-6 mg/kg/day in 1-3 divided doses (N.B: For overweight/obese children ideal weight should be used to calculate dosage).
  1. *For infants 1-12 months old (estimated weight of 4.2-10 kg)*
     1 ml-2.2 ml of Vitcofol syrup, two times a day. 1 ml of syrup provides 6.6 mg of elemental iron and 2.2 ml of syrup provides 14.52 mg of elemental iron.

2. *For children 1-5 years old (estimated weight of 10-18kg)*
   2.2 ml-4 ml of Vitcofol syrup, two times a day. 4 ml of syrup contains 26.4 mg of elemental iron.
3. *For children 5-12 years old (estimated weight of 18-39 kg)*
   4 ml-8.5 ml of Vitcofol syrup, two times a day. 8.8 ml of syrup provides 58 mg of elemental iron.

- Prophylactic dose
  1-2 mg/kg/day in 1-3 divided doses and the maximum dose should not exceed 15 mg/day for infants and 30 mg/day for children.
  1. *For infants 1-12 months old (estimated weight of 4.2-10 kg)*
     0.6 ml-1.5 ml of Vitcofol syrup once a day. 0.6 ml of syrup provides 3.9 mg of elemental iron and 1.5 ml of syrup provides 9.9 mg of elemental iron.
  2. *For children 1-5 years old (estimated weight of 10-18 kg)*
     1.5 ml-2.7 ml of Vitcofol syrup, once a day. 4.5 ml of cough syrup provides 29.7 mg of elemental iron.

Folic acid deficiency/megaloblastic anaemia

<u>*Adults*</u>

- Treatment dose
  0.25-1 mg daily – 2.5 ml (once a day) to 5 ml (twice a day) of Vitcofol syrup.

- Maintenance dose
  1. *Adult*
     0.4 mg daily (4 ml of Vitcofol syrup once a day). 4 ml of syrup provides 0.4 mg of folic acid.
  2. *For pregnant and lactating women*
     0.8 mg daily (8 ml of Vitcofol syrup once daily). 8 ml of syrup provides 0.8 mg of folic acid.

- Prophylaxis dose of megaloblastic anaemia in pregnancy
  0.2 -0.5 mg daily (2-5 ml of Vitcofol syrup once a day). 2 ml of syrup provides 0.2 mg of folic acid and 5 ml of syrup provides 0.5 mg of folic acid.

<u>*Child*</u>

- Treatment dose
  The treatment dose of folic acid is up to 1mg/day (up to 5 ml of Vitcofol syrup twice daily) for children (regardless of age). 5 ml of Vitcofol syrup twice daily provides 1 mg of folic acid.

- Maintenance dose
  1. *For infants 1-12 months old (estimated weight of 4.2-10 kg)*
     0.1 mg/day (1 ml of Vitcofol syrup once a day). 1 ml of syrup provides 0.1 mg of folic acid.
  2. *For children 1-4 years old (estimated weight of 10-16 kg)*
     0.3 mg/day (3 ml of Vitcofol syrup once a day). 3 ml of syrup provides 0.3 mg of folic acid.
  3. *For children above 4 years*

0.4 mg/day (4 ml of Vitcofol syrup once a day). 4 ml of syrup provides 0.4 mg of folic acid.

4.3 Contraindications
Vitcofol is contraindicated in previous hypersensitivity, anaemias associated with ineffective erythropoiesis, marrow hypoplasia, primary (idiopathic) or secondary iron storage disease, intestinal disease, active rheumatoid arthritis, and Addisonian pernicious anaemia.

4.4 Special warnings and precautions for use
Vitcofol should not be used to treat hemolytic anaemia unless an iron-deficient state also exists. Iron should not be administered to patients receiving repeated blood transfusions, since there is a considerable amount of iron in the haemoglobin of transfused erythrocytes.

Vitcofol should be administered with extreme caution to patients with undiagnosed anaemia since folic acid may obscure the diagnosis of pernicious anaemia by alleviating hematologic manifestations of the disease while allowing neurologic complications to progress.

A cyanocobalamin sensitivity history should be obtained from the patient before administration of Vitcofol. Indiscriminate administration of this medicine may mask precise diagnosis. For pernicious anaemia, an adequate dose must be used and the blood picture must be examined regularly at least every three months for 18 months until stabilised and then annually. The increase in nucleic acid degradation produced by administering cyanocobalamin to cyanocobalamin-deficient patients could result in gout.

Excipients
Vitcofol contains sorbitol. The additive effect of concomitantly administered products containing sorbitol/fructose and dietary intake of sorbitol/fructose should be taken into account. The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.

Vitcofol contains sucralose, an artificial sweetener and sugar substitute synthesized by the selective chlorination of sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Vitcofol contains carmoisine which is an azo colouring agent and may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction
Iron reduces the absorption of penicillamine. Iron compounds impair the bioavailability of fluoroquinolones, levodopa, carbidopa, thyroxine and bisphosphonates. The absorption of tetracyclines is severely impaired & efficacy is consequently diminished by iron. Absorption of both iron and zinc is reduced if taken concomitantly. The bioavailability of iron is reduced by the simultaneous ingestion of antacids. Administration of oral iron may increase blood pressure in pregnant patients receiving methyldopa.

Folic acid occasionally reduces plasma levels of anticonvulsants, particularly phenytoin. Co-trimoxazole, chloramphenicol, sulphasalazine, aminopterin, methotrexate, pyrimethamine or sulphonamides may interfere with folate metabolism. Oral chloramphenicol delays plasma iron clearance, incorporation of iron into red blood cells and interferes with erythropoiesis.

Absorption of cyanocobalamin may be reduced by para-aminosalicylic acid, colchicine, biguanides, neomycin, cholestyramine, potassium chloride, methyldopa and cimetidine. Serum levels may be lowered by oral contraceptives. These interactions are unlikely to have clinical significance. Anti-metabolites and most antibiotics invalidate cyanocobalamin (Vitamin B12) assays by microbiological techniques.

4.6 Pregnancy and lactation
There is no precaution except Vitcofol should not be used for the treatment of megaloblastic anaemia during pregnancy unless cyanocobalamin deficiency has been demonstrated. It is unknown whether ferrous fumarate and folic acid/metabolites are excreted in human milk. A risk to newborns/infants cannot be excluded.

No fertility data is available.

4.7 Effects on ability to drive and use machines
Ferrous fumarate/folic acid/cyanocobalamin has no influence on the ability to drive and use machines.

4.8 Undesirable effects
Adverse effects may include upper abdominal discomfort, nausea, metallic taste, heartburn and either constipation or diarrhoea, blackening of the stools, itchy skin eruption, malaise, and bronchospasm.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the e-PV desktop applications (https://drive.google.com/file/d/16hwTz0587ZWtSWadbBAMwQPOD_KSExZP/view) or search for e-PV Mobile applications on the Google Play or Apple App Store.

4.9 Overdose

Symptoms
The main features of overdosage may include abdominal pain, vomiting, diarrhoea and gastrointestinal bleeding (frequent). These may appear within 60 minutes. Cardiovascular collapse with coma may follow. Some improvement may occur after this phase which, in some patients, is followed by recovery. In others, after about 16 hours, deterioration may occur involving diffuse vascular congestion, pulmonary oedema, convulsions, anuria, hypothermia, severe shock, metabolic acidosis, coagulation abnormalities and hypoglycaemia.

Management
Vomiting should be induced immediately, followed as soon as possible by parenteral injection of desferrioxamine mesylate, and then gastric lavage. Fluid replacement is essential. It is helpful to give milk and/or 5 % sodium bicarbonate solution by mouth. Dissolve 2 g desferrioxamine mesylate in 2 to 3 ml of water for injections and give intramuscularly. A solution of 5 g desferrioxamine in 50 to 100 ml of fluid may be left in the

stomach. If desferrioxamine is not available, leave 300 ml of 1 % to 5 % sodium bicarbonate in the stomach.

Recovery may be complicated by long-term sequelae such as hepatic necrosis, pyloric stenosis or acute toxic encephalitis which may lead to CNS damage.

Paediatric population
An acute overdose of oral iron requires emergency treatment. In young children, 200-250 mg/kg of ferrous fumarate is considered to be extremely dangerous.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacological classification: 10.1.4. Medicines affecting the blood: Combinations.

Ferrous fumarate
Ferrous fumarate contains 33 % iron and is moderately soluble in water, stable and almost tasteless. About 80 % of the iron in plasma is delivered to the erythroid marrow to be packaged into new erythrocytes. Iron requirements are determined by obligatory physiological losses and the needs imposed by growth. Therefore, the adult male has a requirement of only 13 ug/kg per day (about 1 mg), whereas the menstruating female requires about 21 ug/kg per day (about 1.4 mg). In the last two trimesters of pregnancy, requirements increase to about 80 ug/kg per day (5 to 6 mg), and the infant has similar requirements due to its rapid growth.

Cyanocobalamin and folic acid
Cyanocobalamin and folic acid are dietary essentials. A deficiency of either vitamin results in defective synthesis of DNA in any cell that attempts chromosomal replication and division. Tissues with the greatest rate of cell turnover show the most dramatic changes, the hemopoietic system is especially sensitive to deficiencies of these vitamins. Clinically the earliest sign of deficiency is megaloblastic anaemia where the derangement in DNA synthesis results in characteristic morphological abnormality of the precursor cells in the bone marrow. Even today, the characteristic abnormality is used both for diagnosis and as a therapeutic guide for the administration of vitamins.

Folic acid is used for the treatment of megaloblastic and macrocytic anaemia resulting from folate deficiency. It is usually indicated in conditions like nutritional macrocytic anaemia & megaloblastic anaemia during pregnancy. Supplemental folic acid may be required to prevent deficiency of the vitamin in patients with conditions that increase folic acid requirements such as pregnancy or nursing.

5.2 Pharmacokinetic properties

Ferrous fumarate
Iron is absorbed chiefly in the duodenum and jejunum. Absorption is aided by the acid secretion of the stomach and when the iron is in a ferrous state. There is marked variability in the absorption of iron. Ferrous salts are at least three times better absorbed than ferric salts. Peak absorption of iron occurs within 1 hour of ingestion and studies with isotopically labelled oral doses have shown that plasma radioactivity may be detected within 10 minutes

of administration. There is a major rapid phase (4 hours), following which the incorporation of a small fraction of residual luminal iron occurs for up to 48 hours after ingestion. There is no enterohepatic circulation.

Folic acid
About 70-80% of a 2 mg oral dose of folic acid is absorbed. It is distributed into plasma and extracellular fluid. Folic acid rapidly appears in the blood, where it is extensively bound to plasma proteins. In plasma, folate is bound weakly to albumin (70%). About 70% of small doses of folate (about 1 mg) are retained and the rest is excreted into urine. With larger doses, most is excreted into the urine about 4 to 5 micrograms is excreted in the urine daily. When larger amounts are absorbed, a high proportion is metabolised in the liver to other active forms of folate and a proportion is stored as reduced and methylated folate. There is an enterohepatic circulation of folate. The retained folate is taken into cells and reduced by dihydrofolate reductase to tetrahydrofolate. Once reduced, folate has additional glutamic acid residues added, a folate pentaglutamate being the dominant intracellular analogue. These polyglutamates are the active coenzymes. Folate enters breast milk which may be beneficial to the infant.

Cyanocobalamin
Physiological amounts (< 2mg doses) given orally are absorbed by binding to proteins present in gastric secretion. These proteins are intrinsic factor (molecular weight 55 000) and R-binder (molecular weight 120 000). In the upper gut the R-binder is degraded by pancreatic enzymes and the cyanocobalamin released binds to free intrinsic factor. The cyanocobalamin-intrinsic factor complex is taken up by specific receptors in the ileum and only cyanocobalamin reaches portal blood. Peak blood levels of cyanocobalamin are attained only 8-10 hours after the oral dose, the delay is due to processes in the enterocyte that are not fully understood. Only about 2 mg of cyanocobalamin is absorbed from a single oral dose by this mechanism.

Oral doses above 2 mg are poorly absorbed by healthy subjects, probably by passive diffusion. Human plasma has three specific cobalamin-binding proteins, transcobalamin II, which is the physiological cobalamin transport protein, and transcobalamin I and III, which are R-binders of unknown function. In addition, cyanocobalamin binds weakly and non-specifically to albumin and globulin fractions. Free cyanocobalamin is excreted in the same way as insulin, that is, it is filtered by the glomerulus and is neither excreted nor absorbed by the renal tubules.

5.3 Preclinical safety data
No data is available.

6. Pharmaceutical particulars

6.1 List of excipients
Guar gum
Sorbitol solution
Polysorbate 80
Glycerin
Sodium methylparaben
Sodium propylparaben
Sucralose

Citric acid monohydrate
Ammonium molybdate
Carmoisine
Orange supreme
Orange oil
Purified water

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Store below 30˚C.

6.5 Nature and contents of the container
The 60 ml suspension is filled in a 100 ml labelled, amber-coloured pet bottle, closed with a ROPP Cap and packed in a carton.

The 180 ml suspension is filled in a 200 ml labelled, amber-coloured pet bottle, closed with a ROPP Cap and packed in a carton.

The 200 ml suspension is filled in a 250 ml labelled, amber-coloured pet bottle, closed with a ROPP Cap and packed in a carton.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. APPLICANT
FDC Limited
142-48, Swami Vivekanand Road
Jogeshwari (West)
Mumbai- 400 102
India

8. MANUFACTURER
FDC Limited, B-8
MIDC Industrial Area, Waluj
Aurangabad – 431 136, Maharashtra
India

9. REGISTRATION DETAILS
Zimbabwe registration number: 2023/10.1.4/6412
Zimbabwe category for distribution: Pharmacy Medicines (P.)

10. DATE OF REVISION OF THE TEXT
August 2023