1. Name Of the Medicinal Product

Vitaferon Plus Blood Tonic

2. Qualitative and Quantitative Composition

Each 5 ml contains:

Ferric Ammonium Citrate……200mg eq. 43mg Elemental iron
Vitamin B1……..2mg
Vitamin B2……1mg
Vitamin B3……6mg
Vitamin B6……..2mg
Vitamin B 12……5mcg
Folic Acid……..0.5 mg

Go to 6.1 for the list of full excipients

3. Pharmaceutical Form

Oral Liquid

A dark brown syrup with sweet taste

4. Clinical Particulars

4.1 Therapeutic indications

Vitaferon plus Blood Tonic is indicated for

- Iron deficiency anaemia due to chronic blood loss, hook-worm infestation, inadequate intake of iron, etc.
- Dimorphic anaemia due to deficiency of Iron, Folic Acid and /or Vitamin B12 (Cyanocobalamin).
- Anaemia of pregnancy and lactation.
- Tonic in general weakness, lack of appetite, rundown conditions and convalescence.
- Post surgery and other debilitated states.

4.2 Posology and method of administration

For Adults: 5ml three times or four times daily or as directed by the physician

Method of administration

Oral

4.3 Contraindications

- Primary (idiopathic) or secondary iron storage disease.
- Anaemia associated with ineffective erythropoiesis, marrow hypoplasia, sideroblastic change, uncomplicated Cyanocobalamin or folate deficiency.

- Intestinal disease (oral iron may aggravate severe acute inflammatory intestinal disease and is ineffective in patients with extensive small intestinal disease eg. celiac sprue.)
- Previous hypersensitivity to any of the ingredient in the syrup.
- Known idiosyncrasy to commonly used excipients.
- Porphyria cutanea tardia.
- Uncontrolled parathyroid disease, sickle cell patients.

4.4 Special warnings and precautions for use

- Iron compounds should not be given to patients receiving repeated blood transfusions or to patients with anaemia not produced by iron deficiency unless iron deficiency is also present.
- Care should be taken in patients with iron storage our iron absorption diseases such as haemochromatosis, hemoglobinopathies or existing gastro-intestinal diseases such as inflammatory bowel disease, intestinal structures and diverticulae.
- Liquid preparations of iron salts should be swallowed through a straw to prevent discoloration of the teeth.

4.5 Interaction with other medicinal products and other forms of interaction

- Compounds containing Calcium and Magnesium including antacids and mineral supplements and bicarbonates, carbonates, oxalates or phosphates, may also impair the absorption of iron by the formation of insoluble complexes.
- Similarly, absorption of both iron & tetracyclines is diminished when they are taken concomitantly by mouth. If treatment with both drugs is required, a time interval of about 2 to 3 hours should be allowed between them.
- Avoid milk and dairy products at least for 2 hours.
- Some agents such as Ascorbic Acid & Citric Acid may actually increase the absorption of iron.
- The response to iron may be delayed in patients receiving concomitant parenteral chloramphenicol therapy.
- Iron salts can decrease the absorption of bisphosphonates, fluoroquinolones, levodopa, methyldopa, penicillamine and tetracycline.
- Iron salts may reduce the efficacy of thyroxine.

4.6 Pregnancy and Lactation

Can be used in Iron deficiency anaemia during Pregnancy and Lactation after considering risk benefit ratio.

4.7 Effects on ability to drive and use machines

Vitaferon Plus Blood Tonic has no influence on the ability to drive or use machines.

4.8 Undesirable effects

Ferric Ammonium Citrate:

In high or toxic doses or poisoning - Gastrointestinal irritation, abdominal pain with nausea, vomiting and either diarrhoea or constipation. Cardiovascular disorders such as

hypotension, tachycardia, metabolic changes including acidosis and hypoglycemia. CNS depression ranging from lethargy to coma.

Folic acid:

Almost non toxic in man and no adverse effects have been reported except a rare and doubtful allergic reaction.

Vitamin B2:

Almost nontoxic in man and no adverse effects have been reported except a rare and doubtful allergic reaction like skin rash, itching, hives, swelling of the face, lips, tongue, or throat

Vitamin B3:

Vitamin B3 is likely safe for most people when taken by mouth. A common minor side effect of niacin is a flushing reaction. This might cause burning, tingling, itching, and redness of the face, arms, and chest, as well as headaches.

Vitamin B6:

When taken by mouth: Vitamin B6 is likely safe when used appropriately. Taking vitamin B6 in doses of 100 mg daily or less is generally considered to be safe. Vitamin B6 is possibly safe when taken in doses of 101-200 mg daily. In some people, vitamin B6 might cause nausea, stomach pain, loss of appetite, headache, and other side effects. Vitamin B6 is possibly unsafe when taken in doses of 500 mg or more daily. High doses of vitamin B6, especially 1000 mg or more daily, might cause brain and nerve problems.

Cyanocobalamin:

No known side effects even with very large doses.

4.9 Overdose

The most sign & Symptoms of overdosage are Gastrointestinal irritation, abdominal pain with nausea, vomiting and either diarrhoea or constipation. Cardiovascular disorders such as hypotension, tachycardia, metabolic changes including acidosis and hypoglycemia. CNS depression ranging from lethargy to coma.

Vomiting is induced immediately followed by parenteral injection of desferroxamine mesylate and then gastric lavage. In the meantime, give milk and/or 5% sodium bicarbonate solution by mouth. Fluid replacement is essential. Other measures include symptomatic management and therapy of metabolic and cardiovascular disorders.

5. Pharmacological Properties

5.1 Pharmacodynamics properties

Pharmacotherapeutics group: Hematinic syrup,

ATC code: B03AE01

Ferric Ammonium Citrate:

Ferric Ammonium Citrate is one of the best-tolerated iron supplements. It rapidly supplements elemental iron so that iron deficiency is quickly controlled, thus leading to faster correction of anaemia and replenishment of tissue iron stores.

Each 5ml of Vitaferon plus Blood Tonic provides 200mg of Ferric Ammonium Citrate that is equivalent to 43mg of elemental iron

Folic Acid:

It is so called because it is present in green leaves, which is chemically pteroylglutamic acid. It is a growth promoter. It helps in the synthesis of Deoxyribose Nucleic Acid (DNA), the building block of life. It is essential for proper maturation of red cells. It helps in inter conversion and metabolism of amino acids.

Vitamin B1:

Thiamine is a vitamin with antioxidant, erythropoietic, cognition-and mood-modulatory, antiatherosclerotic, putative ergogenic, and detoxification activities. Thiamine has been found to protect against lead-induced lipid peroxidation in rat liver and kidney. Thiamine deficiency results in selective neuronal death in animal models. The neuronal death is associated with increased free radical production, suggesting that oxidative stress may play an important early role in brain damage associated with thiamine deficiency. Thiamine plays a key role in intracellular glucose metabolism and it is thought that thiamine inhibits the effect of glucose and insulin on arterial smooth muscle cell proliferation. Inhibition of endothelial cell proliferation may also promote atherosclerosis. Endothelial cells in culture have been found to have a decreased proliferative rate and delayed migration in response to hyperglycemic conditions. Thiamine has been shown to inhibit this effect of glucose on endothelial cells.

Vitamin B3

Niacin is a B vitamin used to treat vitamin deficiencies as well as hyperlipidemia, dyslipidemia, hypertriglyceridemia, and to reduce the risk of myocardial infarctions. Niacin acts to decrease levels of very low-density lipoproteins and low-density lipoproteins, while increasing levels of high-density lipoproteins. Niacin has a wide therapeutic window with usual oral doses between 500mg and 2000mg. Patients with diabetes, renal failure, uncontrolled hypothyroidism, and elderly patients taking niacin with simvastatin or lovastatin are at increased risk of myopathy and rhabdomyolysis.

Vitamin B6:

Vitamin B6, principally in its biologically active coenzyme form pyridoxal 5'-phosphate, is involved in a wide range of biochemical reactions, including the metabolism of amino acids and glycogen, the synthesis of nucleic acids, hemoglobin, sphingomyelin and other sphingolipids, and the synthesis of the neurotransmitters serotonin, dopamine, norepinephrine and gamma-aminobutyric acid (GABA)

Cyanocobalamin:

Cyanocobalamin (Vitamin B12) is a complex organo-metallic compound in which a cobalt atom is placed within a corrin ring. It plays an important role in synthesis of DNA and maturation of red cells. It acts as a co-enzyme in certain steps necessary for genetic replication.

5.2 Pharmacokinetic properties

Iron (Ferric Ammonium Citrate):

Iron irregularly and incompletely absorbed from the gastrointestinal tract, the main sites of absorption being the duodenum and jejunum. Absorption is aided by the acid section of the stomach and by some dietary acids (such as ascorbic acid) and is more readily affected when the iron is in the ferrous state or is part of the haem complex (haem-iron). Absorption is also increased in conditions of iron deficiency or in the fasting state but is decreased if the body stores are overloaded. Only about 5 to 15% of the iron ingested in food is normally absorbed.

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.

Niacin performs a number of functions in the body and so has many mechanisms, not all of which have been fully described.3 Niacin can decrease lipids and apolipoprotein B (apo B)-containing lipoproteins by modulating triglyceride synthesis in the liver, which degrades apo B, or by modulating lipolysis in adipose tissue.3

Vitamin B3

Niacin inhibits hepatocyte diacylglycerol acyltransferase. This action prevents the final step of triglyceride synthesis in hepatocytes, limiting available triglycerides for very low-density lipoproteins (VLDL). This activity also leads to intracellular degradation of apo B and decreased production of low-density lipoproteins, the catabolic product of VLDL.

Niacin also inhibits a high-density lipoprotein (HDL) catabolism receptor, which increases the levels and half life of HDL.

In patients with chronic kidney disease, the Cmax is 0.06μg/mL for a 500mg oral dose, 2.42μg/mL for a 1000mg oral dose, and 4.22μg/mL for a 1500mg oral dose.2 The Tmax is 3.0 hours for a 1000mg or 1500mg oral dose. The AUC is 1.44μg*h/mL for a 500mg oral dose,

6.66µg*h/mL for a 1000mg oral dose, and 12.41µg*h/mL for a 1500mg oral dose. These values did not drastically differ in patients requiring dialysis.

Vitamin B1

It is thought that the mechanism of action of thiamine on endothelial cells is related to a reduction in intracellular protein glycation by redirecting the glycolytic flux. Thiamine is mainly the transport form of the vitamin, while the active forms are phosphorylated thiamine derivatives. Natural derivatives of thiamine phosphate, such as thiamine monophosphate (ThMP), thiamine diphosphate (ThDP), also sometimes called thiamine pyrophosphate (TPP), thiamine triphosphate (ThTP), and thiamine triphosphate (AThTP), that act as coenzymes in addition to each unique biological functions.

Absorbed mainly from duodenum, by both active and passive processes

Vitamin B6:

Vitamin B6 is the collective term for a group of three related compounds, pyridoxine (PN), pyridoxal (PL) and pyridoxamine (PM), and their phosphorylated derivatives, pyridoxine 5'-phosphate (PNP), pyridoxal 5'-phosphate (PLP) and pyridoxamine 5'-phosphate (PMP). Although all six of these compounds should technically be referred to as vitamin B6, the term vitamin B6 is commonly used interchangeably with just one of them, pyridoxine. Vitamin B6, principally in its biologically active coenzyme form pyridoxal 5'-phosphate, is involved in a wide range of biochemical reactions, including the metabolism of amino acids and glycogen, the synthesis of nucleic acids, hemoglobin, sphingomyelin and other sphingolipids, and the synthesis of the neurotransmitters serotonin, dopamine, norepinephrine and gamma-aminobutyric acid (GABA).The B vitamins are readily absorbed from the gastrointestinal tract, except in malabsorption syndromes. Pyridoxine is absorbed mainly in the jejunum. The Cmax of pyridoxine is achieved within 5.5 hours.

Pyridoxine is a prodrug primarily metabolized in the liver. The metabolic scheme for pyridoxine is complex, with formation of primary and secondary metabolites along with interconversion back to pyridoxine. Pyridoxine's major metabolite is 4-pyridoxic acid.

Folic Acid:

Folic acid is rapidly absorbed from the gastro-intestinal tract, mainly from the duodenum and jejunum. Folic acid administered therapeutically enters the portal circulation largely unchanged since it is a poor substrate for reduction by dihydrofolate reductase. It is converted to the metabolically active form 5-methyltetrahydrofolate in the plasma and liver.

The principal storage site of folate is the liver; it is also actively concentrated in the CSF.

Folate undergoes enterohepatic circulation. Folate metabolites are eliminated in the urine and folate in excess of body requirements is excreted unchanged in the urine. Folate is distributed into breast milk. Folic acid is removed by haemodialysis.

Cyanocobalamin:

Cyanocobalamin bind to intrinsic factor, a glycoprotein secreted by the gastric mucosa, and are then actively absorbed from the gastro-intestinal tract. Absorption is impaired in patients with an absence of intrinsic factor, with a malabsorption syndrome or with disease or abnormality of the gut, or after gastrectomy. Absorption from the gastro-intestinal tract can also occur by passive diffusion.

Cyanocobalamin is extensively bound to specific plasma proteins called transcobalamins; transcobalamin II appears to be involved in the rapid transport of the cobalamins to tissues. Cyanocobalamin is stored in the liver, excreted in the bile and undergoes extensive enterohepatic recycling; part of an administered dose is excreted in the urine, most of it in the first 8 hours; urinary excretion, however, accounts for only a small fraction in the reduction of total body stores acquired by dietary means. Cyanocobalamin diffuses across the placenta and also appears in breast milk.

5.3 Preclinical safety data

Toxicology

Iron:

Iron is a general cellular poison and is directly corrosive to the GI mucosa.

Cellular toxicity

The absorption of excessive quantities of ingested iron results in systemic iron toxicity. Severe overdose causes impaired oxidative phosphorylation and mitochondrial dysfunction, which can result in cellular death. The liver is one of the organs most affected by iron toxicity, but other organs such as the heart, kidneys, lungs, and the hematologic systems also may be impaired.

Mild To Moderate Poisoning: Vomiting and diarrhea may occur within 6 hours of ingestion.

severe poisoning: Severe vomiting and diarrhea, lethargy, metabolic acidosis, shock, GI hemorrhage, coma, seizures, hepatotoxicity, and late onset GI strictures.

Folic acid:

The risk of toxicity from folic acid is low, because folate is a water-soluble vitamin and is regularly removed from the body through urine. One potential issue associated with high dosages of folic acid is that it has a masking effect on the diagnosis of pernicious anaemia (vitamin B12 deficiency).

Vitamin B12:

Vitamin B12 is usually considered a non-toxic substance. Even taking it by injection at high doses does not seem to increase the risk for toxicity.

6. Pharmaceutical Particulars

6.1 List of excipients

Sucrose B.P., Sodium Methyl Hydroxybenzoate B.P., Sodium Propyl Hydroxybenzoate B.P., Sorbitol Solution (70%) B.P. (Non- Crystallising), Liquid Glucose USP/NF, Caramel, Sodium Hydroxide B.P., Xanthan gum, Sodium benzoate, Purified Water B.P.

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 container

Vitaferon Plus iron tonic is presented in 200ml pet bottle capped with silver colour ropp cap.

Secondary packaging material: Mono-carton

6.6 Special precautions for disposal

No special requirements.

7. Marketing authorisation holder

Daily Sun Pharmaceutical Company Limited

Plot 3 & 4, Tomori Industrial Estate,

Off Idi-Iroko Road, Ota Ogun State Nigeria

8. Marketing authorisation number(s)

04-4850