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

IVIT-12 INJECTION

(Combination Pack of Vitamin C Injection I.P. (Part 1) & Vitamin B_{12}, Folic acid & Niacinamide Injection (Part 2))

COMPOSITION

Each 1.5 ml ampoule (Part 1) contains:

Vitamin C I.P.	150 mg
Water for Injections I.P.	q.s.

Each 1 ml ampoule (Part 2) contains:

Vitamin B12 I.P.	2500 mcg
Folic acid I.P.	0.7 mg
Niacinamide I.P.	12 mg
Water for Injections I.P.	q.s.

Appropriate overages added to compensate loss on storage.

DESCRIPTION

Vitamin C

It is having a molecular weight of 176.1 and empirical formula of $C_6H_8O_6$.

Vitamin B_{12}

The chemical name is 5,6-dimethyl-benzimidazolyl cyanocobamide; the molecular formula is $C_{63}H_{88}CoN_{14}O_{14}P$. The cobalt content is 4.34%. The molecular weight is 1355.39.

Vitamin B_{12} is present in the body mainly as methylcobalamin and as adenosylcobalamin and hydroxocobalamin. These act as co-enzymes in the trans methylation of homocysteine to methionine; in the isomerisation of methylmalonyl co-enzyme to succinyl co-enzyme and with folate in several metabolic pathways respectively. Deficiency of Vitamin B_{12} interferes with haemopoiesis and produces megaloblastic anaemia.

Folic acid

Folic acid, N-[ρ-[[(2-amino-4-hydroxy-6-pteridinyl) methyl]-amino]benzoyl]-L-glutamic acid, is a B complex vitamin containing a pteridine moiety linked by a methylene bridge to para-aminobenzoic acid, which is joined by a peptide linkage to glutamic acid. Conjugates of folic acid are present in a wide variety of foods, particularly liver, kidneys, yeast, and leafy green vegetables. Commercially available folic acid is prepared synthetically. Folic acid occurs as a yellow or yellowish-orange crystalline powder and is very slightly soluble in water and insoluble in alcohol. Folic acid is readily soluble in dilute solutions of alkali hydroxides and carbonates and solutions of the drug may be prepared with the aid of sodium hydroxide or sodium carbonate, thereby forming the soluble sodium salt of folic acid (sodium folate). Aqueous solutions of folic acid are heat sensitive and rapidly decompose in the presence of light and/or riboflavin; solutions

should be stored in a cool place protected from light.

Niacinamide
Niacin (nicotinic acid) is an essential B complex Vitamin (B_3), whose deficiency results in the clinical syndrome known as pellagra. Nicotinic acid is converted in the body to nicotinamide adenine dinucleotide (NAD) or nicotinamide adenine dinucleotide phosphate (NADP), which function as coenzymes for a wide variety of vital oxidation-reduction reactions.

CLINICAL PHARMACOLOGY

Vitamin C
Vitamin C, a water-soluble vitamin, is essential for the synthesis of collagen and intercellular material.
Ascorbic acid is readily absorbed from the gastrointestinal tract and is widely distributed in the body tissues. Ascorbic acid in excess of the body's needs is rapidly eliminated in the urine.
The most established function of vitamin C in the body is the control of the formation of colloidal intercellular substances. Deficiency of vitamin C leads to scurvy and in the absence of this water-soluble vitamin, a typical nutritional anaemia develops; the vitamin acts directly on the blood-forming centres and is essential for the maturation of the red blood cells.

Vitamin B_{12}
Vitamin $B_{12}$is essential to growth, cell reproduction, hematopoiesis, and nucleoprotein and myelin synthesis.

Cyanocobalamin is quantitatively and rapidly absorbed from intramuscular and subcutaneous sites of injection; the plasma level of the compound reaches its peak within 1 hour after intramuscular injection. Absorbed vitamin $B_{12}$is transported via specific B_{12}binding proteins, transcobalamin I and II to the various tissues. The liver is the main organ for vitamin B_{12}storage.

Within 48 hours after injection of 100 or 1000 mcg of vitamin B12, 50 to 98% of the injected dose may appear in the urine. The major portion is excreted within the first eight hours. Intravenous administration results in even more rapid excretion with little opportunity for liver storage.

Gastrointestinal absorption of vitamin B_{12}depends on the presence of sufficient intrinsic factor and calcium ions. Intrinsic factor deficiency causes pernicious anemia, which may be associated with subacute combined degeneration of the spinal cord. Prompt parenteral administration of vitamin B_{12}prevents progression of neurologic damage.

The average diet supplies about 5 to 15 mcg/day of vitamin B_{12}in a protein-bound form that is available for absorption after normal digestion. Vitamin $B_{12}$is not present in foods of plant origin, but is abundant in foods of animal origin. In people with normal

absorption, deficiencies have been reported only in strict vegetarians who consume no products of animal origin (including no milk products or eggs).

Vitamin $B_{12}$is bound to intrinsic factor during transit through the stomach; separation occurs in the terminal ileum in the presence of calcium, and vitamin B_{12}enters the mucosal cell for absorption. It is then transported by the transcobalamin binding proteins. A small amount (approximately 1% of the total amount ingested) is absorbed by simple diffusion, but this mechanism is adequate only with very large doses. Oral absorption is considered too undependable to rely on in patients with pernicious anemia or other conditions resulting in malabsorption of vitamin B_{12}.

Cyanocobalamin is the most widely used form of vitamin B_{12}, and has hematopoietic activity apparently identical to that of the antianemia factor in purified liver extract. Hydroxycobalamin is equally as effective as Cyanocobalamin, and they share the cobalamin molecular structure.

Folic acid

Folic acid acts on megaloblastic bone marrow to produce a normo-blastic marrow. In man, an exogenous source folate is required for nucleo-protein synthesis and the maintenance of normal erythropoiesis. Folic acid is the precursor of tetrahydrofolic acid, which is involved as a cofactor for transformylation reactions in the biosynthesis of purines and thymidylates of nucleic acids. Impairment of thymidylate synthesis in patients with folic acid deficiency is thought to account for the defective deoxyribonucleic acid (DNA) synthesis that leads to megaloblast formation and megaloblastic and macrocytic anemias.

Niacinamide

Niacinamide, the active ingredient, is the physiologically active form of niacin and is the chemical form of Vitamin B_3 found in virtually all multivitamin products. Though nicotinic acid and nicotinamide are so closely related chemically, they differ somewhat in pharmacological properties. Nicotinic acid products exhibit moderately intense cutaneous vasodilation, resulting frequently in mild headaches and flushing or tingling of the skin, but such reactions have not been observed with nicotinamide. Nicotinic acid has also been used for its effect to lower plasma cholesterol, again a property not shared by nicotinamide.

Nicotinamide has demonstrated beneficial effects on inflammatory acne. It is considered that these effects are related to its significant anti-inflammatory activity.

INDICATIONS

Useful as a co-prescription in the management of chronic diseases like Cardiovascular disorders such as hyperlipidemia, megaloblastic anemias, Malignancy of pancreas or bowel prehypertension/hypertension, coronary artery disease;

Diabetes associated conditions such as insulin reistance, prediabetes, polycystic ovary syndrome, multiple sclerosis; Chronic inflammatory condition such as rheumatoid arthritis; Opthalmological conditions such as cataract, glaucoma, diabetic retinopathy, age related macular degeneration and infertility.

CONTRAINDICATION
Hypersensitivity to any of the components of formulation.

WARNINGS AND PRECAUTIONS
Vitamin C
Increased intake of ascorbic acid over a prolonged period may result in an increase in renal clearance and deficiency may result if it is withdrawn too rapidly. Diabetics, patients prone to recurrent renal calculi, those undergoing stool occult blood tests, and those on sodium-restricted diets or anticoagulant therapy should not take excessive doses of vitamin C over an extended period of time.

Vitamin B_{12}
Patients with early Leber's disease (hereditary optic nerve atrophy) who were treated with Cyanocobalamin suffered severe and swift optic atrophy.
Hypokalemia and sudden death may occur in severe megaloblastic anemia which is treated intensely.

Anaphylactic shock and death have been reported after parenteral vitamin B_{12}administration. An intradermal test dose is recommended before Cyanocobalamin Injection, USP is administered to patients suspected of being sensitive to this drug.

General Precautions: Vitamin B_{12} deficiency that is allowed to progress for longer than 3 months may produce permanent degenerative lesions of the spinal cord. Doses of folic acid greater than 0.1 mg per day may result in hematologic remission in patients with vitamin B_{12}deficiency. Neurologic manifestations will not be prevented with folic acid, and if not treated with vitamin B_{12}, irreversible damage will result.
Doses of Cyanocobalamin exceeding 10 mcg daily may produce hematologic response in patients with folate deficiency. Indiscriminate administration may mask the true diagnosis.

Information for Patients: Patients with pernicious anemia should be informed that they will require monthly injections of vitamin $B_{12}$for the remainder of their lives. Failure to do so will result in return of the anemia and in development of incapacitating and irreversible damage to the nerves of the spinal cord. Also, patients should be warned about the danger of taking folic acid in place of vitamin B_{12}, because the former may prevent anemia but allow progression of subacute combined degeneration.
A vegetarian diet which contains no animal products (including milk products or eggs) does not supply any vitamin B_{12}. Patients following such a diet should be advised to take oral vitamin B_{12} regularly. The need for vitamin B_{12} is increased by pregnancy and lactation. Deficiency has been recognized in infants of vegetarian mothers who were breast fed, even though the mothers had no symptoms of deficiency at the time.

Folic acid
Administration of folic acid alone is improper therapy for pernicious anemia and other megaloblastic anemias in which vitamin B_{12} is deficient.

Folic acid in doses above 0.1 mg daily may obscure pernicious anemia in that hematologic remission can occur while neurologic manifestations remain progressive.
There is a potential danger in administering folic acid to patients with undiagnosed anemia, since folic acid may obscure the diagnosis of pernicious anemia by alleviating the hematologic manifestations of the disease while allowing the neurologic complications to progress. This may result in severe nervous system damage before the correct diagnosis is made. Adequate doses of vitamin B_{12} may prevent, halt, or improve the neurologic changes caused by pernicious anemia.

Niacinamide
Caution should also be used when niacinamide is used in patients with unstable angina or in the acute phase of an MI, particularly when such patients are also receiving vasoactive drugs such as nitrates, calcium channel blockers, or adrenergic blocking agents.
Niacinamide is rapidly metabolized by the liver, and excreted through the kidneys. Niacinamide is contraindicated in patients with significant or unexplained hepatic impairment and should be used with caution in patients with renal impairment. Patients with a past history of jaundice, hepatobiliary disease, or peptic ulcer should be observed closely during niacinamide therapy.

DRUG INTERACTION
Vitamin C
Concomitant administration of aluminium-containing antacids may increase urinary aluminium elimination. Concurrent administration of antacids and ascorbic acid is not recommended, especially in patients with renal insufficiency.
Concomitant administration of aspirin and ascorbic acid may interfere with absorption of ascorbic acid. Renal excretion of salicylate is not affected and does not lead to reduced anti-inflammatory effects of aspirin.
Concurrent administration of ascorbic acid with desferrioxamine enhances urinary iron excretion. Cases of cardiomyopathy and congestive heart failure have been reported in patients with idiopathic haemochromatosis and thalassaemias receiving desferrioxamine who were subsequently given ascorbic acid. Ascorbic acid should be used with caution in these patients and cardiac function monitored.
Ascorbic acid may interfere with biochemical determinations of creatinine, uric acid and glucose in samples of blood and urine.

Vitamin B_{12}
Agents that affect blood products, agents that affect the nervous system, alcohol, Alzheimer's agents, antibiotics (neomycin), anti-seizure agents, aspirin, bile acid sequestrants, birth control pills, cardiovascular agents, chloramphenicol, metformin, nicotine, nitrous oxide, para-aminosalicylic acid, stimulants and zidovudine.

Folic acid
There is evidence that the anticonvulsant action of phenytoin is antagonized by folic acid. A patient whose epilepsy is completely controlled by phenytoin may require increased doses to prevent convulsions if folic acid is given.

Folate deficiency may result from increased loss of folate, as in renal dialysis and/or interference with metabolism (e.g. folic acid antagonists such as methotrexate); the administration of anticonvulsants, such as diphenylhydantoin, primidone, and barbiturates; alcohol consumption and, especially alcoholic cirrhosis; and the administration of pyrimethamine and nitrofurantoin.
False low serum and red cell folate levels may occur if the patient has been taking antibiotics, such as tetracycline, which suppress the growth of Lactobacillus casei.

Niacinamide
Niacin may also interact with agents for the heart, agents that widen blood vessels, agents used for the liver, agents used for seizures, alcohol, androgens, antibiotics, antigout agents, antihistamines, antithyroid agents, aspirin, benzodiazepines, birth control taken by mouth, calcium-channel blockers, cholesterol-lowering agents (bile acid sequestrants, fibrates, HMG-CoA reductase inhibitors), epinephrine, estrogens, ganglionic blocking drugs, griseofulvin, neomycin, nicotine, nonsteroidal anti-inflammatory drugs (NSAIDs), primidone, probucol, procetofene, progestins, pyrazinamide, theophylline, and thyroid hormones.

ADVERSE EFECTS
Vitamin C
Transient mild soreness may occur at the site of intramuscular or subcutaneous injection. Too-rapid intravenous administration of the solution may cause temporary faintness or dizziness.

Vitamin B_{12}
Polycythemia vera, itching; transitory exanthema, Mild transient diarrhea and feeling of swelling of entire body.

Folic acid
Allergic sensitization has been reported following both oral and parenteral administration of folic acid.
Folic acid is relatively non toxic in man. Rare instances of allergic responses to folic acid preparations have been reported and have included erythema, skin rash, itching, general malaise, and respiratory difficulty due to bronchospasm.
One patient experienced symptoms suggesting anaphylaxis following injection of the drug. Gastrointestinal side effects, including anorexia, nausea, abdominal distention, flatulence, and a bitter or bad taste, have been reported in patients receiving 15 mg folic acid daily for 1 month. Other side effects reported in patients receiving 15 mg daily include altered sleep patterns, difficulty in concentrating, irritability, over activity, excitement, mental depression, confusion, and impaired judgment. Decreased vitamin B_{12}serum levels may occur in patients receiving prolonged folic acid therapy.
In an uncontrolled study, orally administered folic acid was reported to increase the incidence of seizures in some epileptic patients receiving phenobarbital, primidone, or diphenyl hydantoin. Another investigator reported decreased diphenyl hydantoin serum levels in folate-deficient patients receiving diphenyl hydantoin who were treated with 5 mg or 15 mg of folic acid daily.

Niacinamide
The most frequently encountered adverse effect reported is dryness of the skin. Other less frequent adverse effects include pruritus, erythema, burning sensation and irritation.

DOSAGES AND ADMINISTRATION
-Dose should be given as directed by the physician.
-IVIT-12 injection must only be administered by the IV or IM route. But before administering the first dose to a new patient, a test dose of IVIT-12 injection should be given.
Direction for Use: Mix the content of ampoules of Part 1 & Part 2 before administration

1. Do not use if suspended material is visible in the solution
2. For I.M/I.V. - Drip

USE IN PREGNANCY, NURSING MOTHER, USE IN CHILDREN AND OLDER PATIENTS
Vitamin C
Ascorbic acid in doses greater than 1g should not be administered during pregnancy as the effect of large doses on the foetus is not known.
No problems are anticipated with the administration of ascorbic acid tablets during lactation.

Vitamin B_{12}
Teratogenic Effects. Pregnancy Category C: Adequate and well-controlled studies have not been done in pregnant women. However, vitamin B12is an essential vitamin and requirements are increased during pregnancy. Amounts of vitamin B12that are recommended by the Food and Nutrition Board, National Academy of Science-National Research Council for pregnant women (4 mcg daily) should be consumed during pregnancy.
Nursing Mothers: Vitamin B12is known to be excreted in human milk. Amounts of vitamin B12that are recommended by the Food and Nutrition Board, National Academy of Science-National Research Council for lactating women (4 mcg daily) should be consumed during lactation.
Pediatric Use: Intake in children should be in the amount (0.5 to 3 mcg daily) recommended by the Food and Nutrition Board, National Academy of Science-National Research Council.

Folic acid
Teratogenic Effects
Pregnancy Category A
Folic acid is usually indicated in the treatment of megaloblastic anemias of pregnancy.
Folic acid requirements are markedly increased during pregnancy, and deficiency will result in fetal damage.
Studies in pregnant women have not shown that folic acid increases the risk of fetal abnormalities if administered during pregnancy. If the drug is used during pregnancy, the possibility of fetal harm appears remote. Because studies cannot rule out the possibility of

harm, however, folic acid should be used during pregnancy only if clearly needed. Folic acid is excreted in the milk of lactating mothers. During lactation, folic acid requirements are markedly increased; however, amounts present in human milk are adequate to fulfill infant requirements, although supplementation may be needed in low birth-weight infants, in those who are breast-fed by mothers with folic acid deficiency (50 μg daily), or in those with infections or prolonged diarrhea.

Niacinamide

Pregnancy

Niacinamide has not been formally assigned to a pregnancy category by the FDA. Niacinamide has been assigned to pregnancy category A by Briggs, et.al, and is considered compatible with pregnancy. The National Academy of Sciences recommended dietary allowance for niacin (which is converted in humans to niacinamide) is 17 mg. and is an essential nutrient required for lipid metabolism, tissue respiration, and glycogenolysis. Niacinamide is actively transported to the fetus. Higher concentrations are found in the fetus and newborn, rather than in the mother. Deficiency of niacinamide in pregnancy is uncommon except in women with poor nutrition. Niacinamide use in excess of the recommended daily allowance (RDA) during normal pregnancy should be avoided.

Breast feeding

Niacin is actively excreted into breast milk. It is unknown if niacinamide is excreted into breast milk, but it is probable that it also is actively transferred. The National Academy of Sciences recommended dietary allowance for niacin is 20 mg. If the diet of the lactating woman adequately supplies this amount, supplementation with niacinamide is not needed. Maternal supplementation with the RDA for niacinamide is recommended only for those patients with inadequate nutritional intake. Niacinamide use in excess of the recommended daily allowance (RDA) during lactation should be avoided.

OVERDOSAGE

Vitamin C, Vitamin B_{12} & Niacinamide

No overdosage has been reported with this drug.

Folic acid

Doses of Folic Acid exceeding the Recommended Dietary Allowance (RDA) should not be included in multivitamin preparations; if therapeutic amounts are necessary, Folic Acid should be given separately.

EXPIRY DATE

Do not use later than the date of expiry.

STORAGE

Store in a cool, dark place away from sunlight**.**

PRESENTATION

Combination pack of vitamin C Injection I.P. & Vitamin B_{12}, Folic acid & Niacinamide Injection.

MARKETED BY:

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IN/IVIT-12 INJECTION/NOV-15/01/PI