NATIONAL AGENCY FOR FOOD & DRUG ADMINISTRATION & CONTROL (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

Product Name

VITBORAH VITAMIN B-COMPLEX INJECTION
(Vitamin B-Complex Injection)

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

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1. Name of the Medicinal Product

VITBORAH VITAMIN B-COMPLEX INJECTION

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2. Qualitative and Quantitative Composition

Each 10ml contains:

Thiamine HCl BP 25 mg

Riboflavin Sodium Phosphate BP 2 mg

Pyridoxine HCl BP 2.5 mg

Niacinamide BP 50 mg

D-Panthenol USP 5 mg

Benzyl Alcohol BP 2%v/v

(as preservative)

Water for Injection BP q.s.

3. Pharmaceutical Form

Injection

4. Clinical Particulars

4.1 Therapeutic indications

Vitamin B complex is indicated in following diseases, manifesting with a vitamine B deficiency: neuritis; alcohol, toxic, and post infectious polyneuritis; diabetic polineuropathy; neuralgia; sciatica; central spastic conditions; myasthenia; paresthesia; atherosclerosis; Wernicke's encephalopathy; vegetative neurosis; dermatitis; neurodermatitis; psoriasis; lupus erythematodes; furunculosis; stomatitis; cheilitis; glositis; colitis; hepatitis; chronic alcohol abuse; asthenia; anemia; intoxications.

4.2 Posology and method of administration

Dosage and Administration

Usually 0.25 to 2ml by intramuscular or slow intravenous injection. High concentrations given intravenously may be diluted using parenteral infusion solutions.

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4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients

4.4 Special warning and special precaution for use

Anaphylactogenesis may occur with parenteral thiamine. Use with caution. An intradermal test dose is recommended prior to administration in patients suspected of being sensitive to the drug.

4.5 Interaction with other medicinal products and form of interaction

Some medication may interact with vitamin B complex. Before using this product, tell your doctor or pharmacist of all prescription and nonprescription/herbal products you may use, especially of: altretamine, cisplatin, certain antibiotics (e.g., chloramphenicol), certain anti-seizure drugs (e.g., phenytoin), levodopa, other vitamin/nutritional supplements.

Consult with your doctor about any medications you are taking, before your treatment with vitamin B complex injection.

4.6 Pregnancy and lactation

Vitamins from B group are generally recommended during pregnancy and breastfeeding as per individual requirement. These vitamins pass through breast milk to the infant. No specific safety data could be identified. Physician’s advice before use is recommended.

4.7 Effects on ability to drive and use machines

Not applicable

4.8 Undesirable effects

Mild transient diarrhea, polycythemia vera, peripheral vascular thrombosis, itching transitory exanthema, feeling of swelling of entire body, anaphylactic shock and death. Sensitivity to the ingredients listed may occur. Use should be discontinued upon observance of any untoward reaction. Pain upon intramuscular injection may be noted.

4.9 Overdose

Symptoms of overdose include thirst, flushing of the skin, and abdominal pain, and dizziness, redness of the skin, excessive urination and diarrhea. These symptoms have to be reported to the medical health professional. Seek medical help urgently.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Thiamine, in the form of thiamine pyrophosphate, is the coenzyme for decarboxylation of □-ketoglutaric acid. It also participates along with other coenzymes, i.e. lipoic acid, coenzyme A, FAD and NAD, in the oxidative decarboxylation of pyruvic acid, which leads to the formation of acetyl CoA.

Thiamine pyrophosphate is also the coenzyme of transketolase. In thiamine deficiency, the hexose monophosphate pathway of glucose oxidation is retarded at the level of the transketolase, so pentose sugars accumulate to levels three times the normal.

Thiamine deficiency affects the peripheral nervous system, the gastrointestinal tract, and the cardiovascular system. This vitamin is necessary for the optimal growth of infants and children. A heatlabile enzyme, thiaminase, present in raw fish destroys its activity. Chastek paralysis occurs in foxes fed a diet containing 10% or more of uncooked fish, due to the thiaminase in raw fish. Mild deficiencies of B1 may occur even with apparently adequate diets, especially when energy needs are increased due to hyperthyroidism or increased carbohydrate intake.

Vitamin B2 (Riboflavin)

Riboflavin is inactive until phosphorylated. Flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) are its active forms and these are involved as coenzymes in the respiratory chain. FAD and FMN influence hydrogen transport in oxidative enzyme systems such as cytochrome C reductase, succinic dehydrogenase and xanthine oxidase. Riboflavin is converted to FMN and FAD by two enzyme-catalysed reactions:

Riboflavin + ATP → FMN + ADP

FMN + ATP → FAD + PP

FMN and FAD are coenzymes for a wide variety of respiratory flavoproteins, some of which also require metals.

Thyroid hormones, corticotrophins and aldosterone enhance the formation of FMN and FAD, while phenothiazines and tricyclic antidepressants inhibit FAD formation. Boric acid increases the excretion of riboflavin.

The requirement for riboflavin depends on the carbohydrate intake and is increased during pregnancy, lactation and in women taking oral contraceptive agents

Vitamin B6 (Pyridoxine)

Vitamin B6 has two main active analogues, i.e. pyridoxal and pyridoxamine, whereas the inactive analogues are norvitamin B6, 4- pyridoxic acid, and 5-pyridoxic acid.

Vitamin B6 is antagonized by various drugs such as 4-deoxypyridoxine, 4-methoxypyridoxine, toxopyrimidine, penicillamine, semicarbazide, isoniazid, oestrogen and Fe3 +. Pyridoxal phosphate is mainly involved as a coenzyme, especially in the metabolic transformation of amino acids including decarboxylation, transamination and racemization.

In the metabolism of tryptophan, vitamin B6 is involved in a number of enzymatic reactions. In vitamin B6-deficient humans and animals, a number of metabolites of tryptophan, especially xanthurenic acid, are excreted in urine in abnormally large quantities. Pyridoxine deficiency in rats is accompanied by a lowered threshold for electroshock-induced tonic-clonic seizures. This is reversed by pyridoxine. The tryptophan loading test has been used to assess vitamin B6 status. This test is based on the reduction in kynureninase activity due to a deficiency of its cofactor, pyridoxal phosphate. The excretion, specifically of xanthurenic acid and possibly also of kynurenine and hydroxy-kynurenine is measured before and after administration of a dose of tryptophan (l-tryptophan 10 g or 100 mg/kg body weight) using a 24-hours collection of urine.

A lower suggested dose of tryptophan (2 g) does not produce sufficient challenge to the pathway tested. The tryptophan load test is not a reliable indicator of vitamin B6 status in persons receiving oestrogens or with increased secretion of glucocorticoids.

Vitamin B6 is a cofactor in the conversion of tryptophan to 5-hydroxytryptamine (5HT) and of methionine to cysteine.

Pyridoxine is capable of modifying the action of steroid hormones in vivo by interacting with the steroid-receptor complexes.

Biochemical interaction occurs between pyridoxal phosphate and certain drugs and toxins. Isoniazid increases urinary excretion of vitamin B6 and prolonged use of penicillamine has caused deficiency of vitamin B6. The drugs cycloserine and hydralazine are also antagonists of vitamin B6. Administration of the vitamin reduces the neurological side effects associated with the use of these agents.

Nicotinamide (Niacin)

Nicotinamide is an essential nutrient. The term `niacin' is often used to refer to both nicotinamide and nicotinic acid; some use niacin as a synonym for nicotinic acid, which can also be converted to the coenzyme forms.

The significant hypolipidaemic and vasodilatory effects of nicotinic acid are not shared by nicotinamide.

Chronic dietary deficiency of niacin results in the disorder pellagra, which is characterized by dermatitis, diarrhoea, dementia, and ultimately death.

Administration of the antimetabolite , 6-aminonicotinamide, to mice produced pathologic lesions of the skin, intestine, and central nervous system that were characteristic of those described in human pellagra. Nicotinamide is needed for the coenzymes NAD and NADP that catalyse tissue oxidation-reduction reactions.

Recommended dietary allowances for adults range from 13 to 18 mg daily. Some dietary tryptophan is converted to nicotinamide by a vitamin B-dependent pathway. For estimating dietary requirement, 60 mg of tryptophan is considered equivalent to 1 mg of niacin, although the efficacy of conversion varies among individuals. Dietary requirements for niacin are usually estimated on the basis of energy expenditure, e.g. for adults, 6.6 mg/1000 kcal.

Pantothenic Acid (Panthenol)

Pantothenic acid is an essential nutrient. However, naturally occurring deficiency has rarely been observed, probably because of its ubiquity in plant and animal tissues - the name of the vitamin is derived from the Greek word pantos, which means `everywhere'. Pantothenic acid deficiency has been produced experimentally in several animal species, but there is considerable species variability in its manifestations.

In chickens, pantothenic acid deficiency produces skin lesions similar to pellagra. Pantothenic acid deficiency leads to greying of the hair in black rats but is not involved in greying of human hair. Adrenocortical insufficiency and neuromuscular degeneration may be seen in some species. Pantothenic acid is converted in the body into coenzyme A which involves a series of enzyme-catalysed reactions.

5.2 Pharmacokinetic properties

Vitamin B1 (Thiamine)

Thiamine is well absorbed from the gastrointestinal tract and widely distributed throughout the body. At low thiamine concentrations, thiamine transport appears to be a saturable, active process. In contrast, at high or pharmacological doses transport is mainly by passive diffusion. Thiamine is rapidly absorbed from the upper small intestine. Thiamine is not stored in the body to any appreciable extent. Excess ingested thiamine appears in urine as intact thiamine or as pyrimidine which arises from degradation of the thiamine molecule.

The plasma half life of thiamine is 24 h, whereas its half life in the body is 10 - 20 days. Normal levels of this vitamin in the blood are 0.2 - 0.4 µg/l in blood and 3.6 µg/g in brain. Human breast milk contains 230 µg/l of thiamine.

Metabolism

Thiamine is not stored to any great extent in the body. Phosphorylated forms are present in all cells. Excess ingested vitamin is excreted in the urine as the free vitamin or a metabolite. Thiamine phosphorylated to the active coenzyme, thiamine pyrophosphate (TPP), which functions as cocarboxylase for various reactions in carbohydrate metabolism, including the transketolase reaction in the direct oxidative pathway of glucose metabolism.

Vitamin B2 (Riboflavin)

Riboflavin is readily absorbed from the gastrointestinal tract, and in circulation it is bound to plasma proteins. Although riboflavin is widely distributed to all tissues, little is stored in the body. Amounts in excess of the body's requirement are excreted in the urine. Riboflavin excretion in the faeces represents biosynthesis of this vitamin by micro- organisms in the large intestine. There is little evidence of its reabsorption from the large intestine.

Renal clearance of riboflavin involves renal tubular secretion as well as glomerular filtration and exceeds endogenous creatine clearance by up to three times. Clearance is reduced at low serum concentrations of riboflavin. Sixty per cent of the riboflavin in serum is bound to serum proteins. Prior administration of probenecid decreases the renal clearance of riboflavin but does not affect its protein binding.

Riboflavin is readily absorbed from the upper gastrointestinal tract by a specific transport mechanism involving phosphorylation of the vitamin to FMN. Here, as in other tissues, riboflavin is converted to FMN by flavokinase, a reaction that is sensitive to thyroid hormone status and inhibited by chlorpromazine and by tricyclic antidepressants. The riboflavin content of human milk is 300µg/l.

Metabolism

When riboflavin is ingested in amounts approximating the minimum daily requirement most of it is utilized in various tissues with only 9% appearing in the urine. Larger doses of riboflavin are excreted in the urine largely unchanged. It is not stored in body tissues to any great extent. Riboflavin is converted to FMN and FAD in the liver after its absorption through the gastrointestinal tract. Patients with hepatitis and cirrhosis of liver and those given probenecid have reduced absorption of riboflavin. Riboflavin in the form of FMN and FAD is phosphorylated in the intestinal mucosa during absorption and stored in small quantities in liver, spleen, kidney and heart muscle.

FMN and FAD are mainly involved in the electron transport chain and form a link between the pyridine nucleotide system and the cytochrome system. Xanthine oxidase flavoprotein, which converts hypoxanthine to uric acid and amino acid

oxidases, which convert amino acids to ammonia and keto acids, require riboflavin coenzymes. The flavoproteins are mainly concerned with hydrogen transport (oxidation). Excess riboflavin is excreted in urine as such and there is no known metabolite with pharmacological activity.

Vitamin B6 (Pyridoxine)

All three forms of vitamin B6 (pyridoxine, pyridoxal and pyridoxamine) are readily absorbed from the gastrointestinal tract. In tissue, they are present primarily as 5-phosphorylated derivatives of pyridoxal and pyridoxamine. Muscle seems to be a major storage site for pyridoxal phosphate in the body. About 50% of total body pyridoxal phosphate is present in the muscle, bound to glycogen phosphorylase. Pyridoxic acid is the major excretory metabolite in urine.

All three forms of vitamin B6, i.e. pyridoxine, pyridoxal and pyridoxamine, are converted to the active form pyridoxal phosphate in the body. The half life of the pyridoxine ranges from 15 to 20 days. It is degraded in the liver to 4-pyridoxic acid which is excreted by the kidney. 5% of the ingested dose of vitamin B6 is excreted as follows: urine: 4-pyridoxic acid (0.6 - 11.2 mg daily), pyridoxal (0.005 - 0.04 mg daily) and pyridoxamine (0.003 -0.20 mg daily); faeces (0.003 - 0.20 mg daily).

Pyridoxine is not significantly bound to plasma proteins. The phosphorylated vitamins appear to bind to plasma proteins and haemoglobin. Uptake of pyridoxine by brain appears to be by a saturable process.

Pooled samples of human breast milk contained 15 - 20 µg/l of vitamin B6.

Metabolism

The liver plays a major role in the metabolism of pyridoxine, pyridoxal and pyridoxamine, which are all phosphorylated by pyridoxal kinase. Pyridoxine phosphate is oxidized to the active coenzyme form, pyridoxal 5-phosphate, by an enzyme found mainly in liver. Pyridoxal 5-phosphate interconverts with pyridoxamine 5-phosphate through enzymatic transamination. The phosphorylated forms are hydrolysed by phosphatases. Plasma levels of vitamin B6 reflect the liver concentrations.

Pyridoxal is oxidized in the liver to pyridoxic acid, the main excretory form of pyridoxine. Pyridoxal 5-phosphate (PLP) is the coenzyme for more than 100 enzymes, with vital roles in intermediary metabolism. Therefore, at first sight, it seems unlikely that a mutation affecting formation or accumulation of PLP would be compatible with life. However, such a possibility cannot yet be excluded, since a partial reduction of available PLP may lead to reduced activity of a few enzymes due

to the widely varying degrees of binding of the pyridoxal phosphate to pyridoxine apoenzymes.

Nicotinamide (Niacin)

In the diet, niacin is present mainly as the coenzyme forms NAD(H) and NADP(H). The bioavailability of food forms of niacin varies significantly, and bound forms in wheat and corn may be largely unavailable. NAD has been demonstrated to undergo extensive digestion prior to intestinal absorption. In the rat, it was demonstrated that NAD was first converted to nicotinamide ribonucleotide by a pyrophosphatase, with subsequent rapid hydrolysis of the nicotinamide ribonucleotide to nicotinamide riboside, which accumulated in the intestinal lumen. The rate-limiting step was conversion of nicotinamide riboside to nicotinamide.

The mechanism of intestinal absorption of nicotinamide remains controversial. Many animal studies suggest passive diffusion, whereas others support carrier-mediated facilitated diffusion.

Conversion of nicotinamide to coenzyme forms in the intestine complicates interpretation of transport data. Perfusion studies in the rat indicated that nicotinamide was readily absorbed, more rapidly than nicotinic acid.

Nicotinamide is the major circulating form of the vitamin. It is readily taken up into tissues and utilized for synthesis of the coenzyme forms. The liver plays a major role in regulating nicotinamide metabolism. Newly ingested nicotinamide appears to enter a hepatic storage pool or NAD.

Metabolism

Nicotinamide is converted to NAD and NADP enzymatically via the Dietrich pathway. Nicotinamide ribonucleotide (NMN) is an intermediate in the pathway and 5-phosphoribosyl-1-pyrophosphate and ATP are cosubstrates. Nicotinamide is degraded in liver and other organs to a number of products that are excreted in the urine, including N- methylnicotinamide, N-methyl-2-pyridone-5-carboxamide, N-methyl-4-yridone-5-carboxamide and nicotinamide-N-oxide. At doses of less than 1000 mg, the 2-pyridone is the major excretory product, whereas at a dose of 3000 mg daily N-methylnicotinamide pre-dominates and some free nicotinamide appears in urine.

Pantothenic Acid (Panthenol)

Following oral administration pantothenic acid appears to be rapidly absorbed and distributed with peak plasma concentrations occurring at 2.5 h. Based on urinary excretion data, the absorption of pantothenic acid in an average American diet was estimated to range from 40% to 61% (averaging 50%) relative to that of the pure

vitamin, for healthy male volunteers receiving diets containing 8.2 - 11.5 mg daily. In the rat intestine, bound forms of pantothenic acid are converted to free pantothenic acid, which is then absorbed, Post-prandially, about 40% of absorbed pantothenic acid is recovered in muscle and 10% in liver.

Pantothenic acid transport has been characterized in experimental animal studies. At pharmacological concentrations in the rat, intestinal absorption of pantothenic acid is consistent with simple diffusion. However, in other tissues, pantothenate transport appears to occur by a saturable mechanism. In the rat hepatocyte, pantothenate uptake kinetics are consistent with sodium cotransport with an apparent Km of 11 µM. Ouabain and other metabolic poisons inhibit uptake but pantothenate preloading does not. Pantothenate uptake by rat renal brush border membrane vesicles is also consistent with a sodium-dependent active transport process with an apparent Km of 7.3 µM. In rat adipocytes, pantothenate uptake is saturable and energy dependent. In addition, in vivo pantothenic acid enters and leaves the rabbit central nervous system by saturable transport systems, with relatively slow conversion of pantothenic acid to coenzyme A.

Pantothenic acid is present in all tissues, at concentrations ranging from 2 to 45 µg/g. Cardiac muscle, liver, adrenal glands, heart and brain contain the highest concentrations. The vitamin is present in both free and bound forms, the latter primarily coenzyme A and acyl carrier protein.

Urinary excretion of pantothenic acid is related to the dietary intake. Excretion of less than 1 mg daily is abnormally low for the adult, as the normal range is 2 - 7 mg daily in adults and 2 - 3 mg daily in children. The vitamin is excreted primarily as free pantothenic acid.

Serum contains free pantothenic acid, while in red cells, most of the vitamin is present as coenzyme A. Total pantothenic acid (free plus bound forms) in whole blood ranges from 500 to 1000 µg/l, with values below 100 µg/l considered abnormal. Serum values around 10 - 20 µg/l have been reported.

Results of kinetic studies using physiological doses of pantothenic acid are not available. However, when large oral doses of pantethine, a conjugate converted to pantothenate during absorption, are given to cystinotic children, pharmacokinetic analysis of plasma and urinary pantothenic acid concentration data is consistent with rapid absorption and distribution, but slow excretion (half life = 28 h). Total body storage under pantothenic acid loading (70 - 1000 mg/kg) is significant, about 25 mg/kg body weight. The data are consistent with an open two-compartment model with slow elimination.

Metabolism

Pantothenic acid is converted to coenzyme A enzymatically via the following intermediates: 4'-phosphopantothenic acid, 4'-phosphopantothenyl cysteine, 4'-phosphopantetheine, dephosphocoenzyme A, and coenzyme A. ATP and cysteine are co-substrates in the pathway. The first step, catalysed by pantothenate kinase, is rate-controlling in all tissues studied and is inhibited by coenzyme A and its acyl esters.

In animal studies, fasting, refeeding and diabetes have been associated with changes in the rate of coenzyme A synthesis. Coenzyme A is degraded to pantothenic acid and cysteamine; however, regulation of this pathway is poorly understood. Most pantothenic acid in the urine is present as the unchanged compound.

5.3 Preclinical Studies

Not applicable

6.0 PHARMACEUTICAL EXCIPIENTS

6.1 List of excipients

1. Benzyl Alcohol BP
2. Propylene Glycol BP
3. Polyethylene Glycol 400 BP
4. Sodium Chloride BP
5. Thiourea BP
6. E.D.T.A. Sodium BP
7. Polysorbate-80 BP
8. Water for Injection BP

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 Months

6.4 Special precaution for storage

Store at temperature not exceeding 30°C. Protect from light.

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6.5 Nature contents of container

10 ml vial

6.6 Instruction for use handling and disposal

Keep out of reach of children.

7. Manufacturer name

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8. Marketing Authority

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