PRODUCT INFORMATION LEAFLET (PRESCRIBING INFORMATIONS)

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POLYBION A INJECTION

Injection of Vitamin B1, B6, B12, Nicotinamide and D-Panthenol

COMPOSITION:

Each 2 ml ampoule contains:
Thiamine Hydrochloride IP……100 mg
Pyridoxine Hydrochloride IP……. 100 mg
Cyanocobalamin IP ……1000 mcg
Nicotinamide IP …… 100 mg
D-Panthenol IP …….. 50 mg
Benzyl Alcohol IP (as preservative)…… 2% w/v
Water for Injection IP ……. Q.S.

List of Excipients
Di-Sodium EDTA IP, Thiourea

PHARMACEUTICAL FORM

POLYBION A INJECTION contains Thiamine Hydrochloride, Pyridoxine Hydrochloride, Cyanocobalamin, Nicotinamide and D-Panthenol as active ingredients.

PHARMACOLOGICAL PROPERTIES

PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group:

Thiamine Hydrochloride: Vitamin B1

Pyridoxine Hydrochloride: Vitamin B6 analogue, water-soluble vitamin

Cyanocobalamin: Vitamin B12 analogue

Nicotinamide: Vitamin B3

D-Panthenol: Vitamin B5 analogue

Therapeutic indications:

Neurological diseases caused by severe vitamin B deficiencies that cannot be remedied by means of oral therapy, diabetic neuropathy, Wernicke-Korsakoff syndrome, Pellagra, pernicious anemia with or without neurological complications. Other macrocytic, megaloblastic anemia where etiology suggests malabsorption of vitamin B12 such as; following gastrectomy, gastric carcinoma, megaloblastic anemia associated with such gastrointestinal disorders as sprue syndrome, blind loops and anastomoses and fish tapeworm.

Posology and method of administration:

Adults and children aged 14 years and above:

2ml ampoule for IM or IV use

IM i.e. intramuscular administration: Inject in gluteal muscle of the buttock or deltoid muscle of the upper arm or vastus lateralis muscle of the thigh

IV i.e. intravenous administration should occur via slow injection into the IV catheter or should be added to an infusion solution by injecting the solution for injection into the port of the infusion bag

Duration:

The duration of treatment should be assessed by the physician depending on the condition of the patient.

MECHANISM OF ACTION

Thiamine Hydrochloride

In blood, the thiamine diphosphokinase enzyme converts thiamine into its active form, thiamine pyrophosphate (TPP). TPP plays different roles during different steps of metabolism, glycolysis, Krebs cycle, and pentose phosphate pathway. TPP works with enzyme functions during the metabolism of carbohydrates, lipids and, branched-chain amino acids. TPP acts as a cofactor at several steps during glycolysis and oxidative decarboxylation of carbohydrates. TPP acts as a coenzyme for the mitochondrial enzyme complexes such as α-ketoglutarate dehydrogenase and pyruvate dehydrogenase. These enzymes have a critical role in the Krebs cycle and tricarboxylic acid cycle.

Thiamine deficiency decreases the activity of these enzymes, which impairs the conversion of lactate into pyruvate, leading to the accumulation of lactic acid. Lactic acidosis may cause focal damage to certain brain structures such as mamillary bodies and posteromedial thalamus.

Apart from its metabolic role as a coenzyme, thiamine plays a role in neurotransmitter function and in nerve conduction. In high doses, thiamine suppresses the transmission of neural stimuli and thus can have an analgesic effect. Early stages of thiamine deficiency may be accompanied by non-specific symptoms that may be overlooked or easily misinterpreted. The clinical signs of deficiency include anorexia; weight loss; mental changes such as apathy, decrease in short-

term memory, confusion and irritability; muscle weakness; and cardiovascular effects such as an enlarged heart.

Cardiac failure, muscle weakness, peripheral and central neuropathy are functional consequences of severe thiamine deficiency. Clinical manifestations of beriberi (severe thiamine deficiency) vary with age. Adults may present with dry (paralytic or nervous), wet (cardiac), or cerebral (Wernicke-Korsakoff syndrome) forms of beriberi.

Pyridoxine Hydrochloride

Vitamin B6 (pyridoxine, pyridoxal, and pyridoxamine) forms are readily absorbed by passive diffusion in the jejunum and ileum, while alpha-glucosidases are expressed and located in the duodenum. The studies suggest that the blood glucose lowering effect of pyridoxine is possibly due to the α-glucosidase inhibitory activities. Furthermore, pyridoxine has high activity of enzyme inhibition (e.g. sucrase, maltase, and glucoamylase).

Recent clinical studies have revealed that hyperhomocysteinemia exaggerates the prevalence of peripheral neuropathy (PN) in diabetics and exacerbates any preexisting diabetic neuropathy. The notion of hyperhomocysteinemia as an independent variable associated with increased prevalence of diabetic PN has been supported by various clinical studies. It was estimated in a recent study that for each 1-mmol/L increase in Hcy (homocysteine), there is a 7.1% increased risk in diabetic autonomic neuropathy. Increased levels of homocysteine are also considered important biomarkers of cardiovascular diseases. Plasma total homocysteine levels tend to be higher in women with clinical and biochemical deficiency of vitamin B6 and therapy with pyridoxine reduced its level significantly.

Pyridoxine is required for the synthesis of the neurotransmitters, serotonin and noradrenaline, and for myelin formation. It functions as a coenzyme in the metabolism of amino acid, glycogen and sphingoid bases.

Cyanocobalamin

Oral cyanocobalamin absorption occurs through the small intestine after binding to intrinsic factor and other cobalamin binding proteins. When given via the parenteral route, it reaches the blood immediately. In the blood, it attaches itself to plasma proteins. Tissues absorb vitamin B12 by specific B12 binding proteins, transcobalamin I and II, allowing it to enter the cells. Most of the vitamin is stored in the liver. Vitamin B12 is essential for DNA synthesis and energy production, particularly in erythroid progenitor cells.

Vitamin B12 serves as a cofactor for two vital enzymes in the body: methylmalonyl-CoA mutase and methionine synthase. These methylation reactions are responsible for annealing Okazaki fragments during DNA synthesis. Methionine synthase is essential for the synthesis of purines and pyrimidines that form DNA. L-methylmalonyl-CoA mutase converts L-methylmalonyl-CoA to succinyl-CoA in the degradation of propionate, an important reaction required for both fat and protein metabolism. It is a lack of vitamin B12 cofactor in the above reaction and the resulting accumulation of methylmalonyl CoA that is believed to be responsible for the neurological manifestations of B12 deficiency. Succinyl-CoA is also necessary for the synthesis of hemoglobin. The replenishment causes total improvement of megaloblastic anemia and the gastrointestinal manifestations of vitamin B12 deficiency. The neurological symptoms in vitamin B12 deficiency improve upon cyanocobalamin administration, but the level of improvement depends on the duration and severity of the

deficiency. The reported but unconfirmed mechanism of action of hydroxocobalamin in vasoplegic shock is direct inhibition of nitric oxide and inhibition of guanylate cyclase.

Nicotinamide

Niacinamide, also known as nicotinamide, is a water soluble amide of nicotinic acid. Niacinamide acts as an antioxidant by preventing NAD depletion during DNA repair by inhibiting poly (ADP-ribose) polymerase (PARP), which also modulates major histocompatibility complex (MHC) class II expression. Niacinamide inhibits free radical formation and facilitates beta-cell regeneration in vivo and in vitro. Additional protection from macrophage toxins may be involved in prevention of type 1 diabetes. Specifically, niacinamide has been shown, via PARP inhibition, to protect pancreatic islet-cell lysis after exposure to oxygen free radicals and nitric oxide. Niacinamide has also been found to stimulate GABA receptors, without binding to the receptor sites, thus creating a benzodiazepine-like effect. Anti-inflammatory action affecting neutrophil chemotaxis has been reported for niacinamide. Additionally, due to its inhibition of ADP-ribosylation, niacinamide has been shown to suppress cytokinemediated induction of nitric oxide synthase in a number of cells, thus effecting interleukin-1-exposed chondrocytes, resulting in decreased inflammation.

D-Panthenol

D-Panthenol is an alcohol derivative of pantothenic acid, a component of the B complex vitamins and an essential component of a normally functioning epithelium. D-Panthenol is enzymatically cleaved to form pantothenic acid, which is an essential component of Coenzyme A, which acts as a cofactor in many enzymatic reactions that are important for protein metabolism in the epithelium.

Vitamin B5 is exclusively a precursor in the synthesis of CoA and thus only directly affects this metabolic pathway. CoA has a role in hundreds of human biochemical reactions such as cell growth, intermediary metabolism, and neurotransmitter synthesis. The structure of CoA functions as a carbonyl-activating group and as an acyl group carrier to help facilitate these various reactions.

PHARMACOKINETIC PROPERTIES

Thiamine Hydrochloride

Thiamine is rapidly absorbed in humans, largely in the proximal small intestine. There are two mechanisms, one by a carrier mediated transport at low physiological concentrations (<2μM), one by passive diffusion at higher concentrations. Absorption is typically high, but intestinal absorption in humans is rate limiting.

Distribution: The average total amount of thiamine in an adult is approximately 30mg. In general the heart has the highest concentration (0.28-0.79mg per 100g), followed by kidney (0.24-0.58mg per 100g), liver (0.20-0.76mg per 100g), and brain (0.14-0.44mg per 100g). In the spinal cord and the brain, the thiamine level is about double that of peripheral nerves. The whole-blood thiamine content varies from 5 to 12μg per 100 ml, 90% of which is in the red cells and leukocytes. Leukocytes have a 10 fold higher concentration than red cells. Thiamine transport across the blood-brain barrier involves two different mechanisms. The saturable

mechanism at the blood-brain barrier, however, differs from the energy-dependent mechanism described in the gut, and from the active transport system described in cerebral cortex cells, which may be dependent upon membrane-bound phosphatases.

Metabolism: Thiamine is quickly converted to the diphosphate and to a smaller extent the triphosphate esters in the tissues. All thiamine in excess of tissue needs, as well as binding and storage capacity, is rapidly excreted in the urine in the free form. Stimulation of nerves causes the release of thiamine or the monophosphate with a concomitant decrease in the tri- and diphosphates.

Excretion: Thiamine is excreted in the urine. The half-life of thiamine in the body is 10-20 days. In addition to free thiamine and a small amount of thiamine diphosphate, thiochrome, and thiamine disulfide, about 20 metabolites of thiamine have been reported in the urine of rats and humans but only six have been conclusively identified.

Pyridoxine Hydrochloride

Pyridoxine is administered orally and by intramuscular or intravenous injection. Vitamin B6 is stored in the liver, with small amounts in the brain and muscles. The total body storage for adults is between 16 to 27 mg. Pyridoxal crosses the placenta, with fetal concentrations five times that of maternal plasma concentrations. Pyridoxal and pyridoxal phosphate are the primary forms of vitamin B6 in the blood. Pyridoxal phosphate is 100% protein-bound. The half-life of pyridoxine is 15 to 20 days. Conversion of pyridoxine to pyridoxal phosphate and pyridoxamine to pyridoxamine phosphate takes place in erythrocytes. Pyridoxine is also phosphorylated in the liver. Pyridoxal is oxidized in the liver to produce 4-pyridoxic acid, which is excreted in the urine. After intravenous infusion of pyridoxine 100 mg over six hours in adult patients, pyridoxal phosphate (PLP) plasma and erythrocyte concentrations increased rapidly from 37 nmol/L to 2183 nmol/L in the plasma and undetectable to 5593 nmol/L in erythrocytes. Peak concentrations were achieved at the end of the infusion.

Cyanocobalamin

Absorption: Vitamins B12 is irregularly absorbed from the distal small intestine following oral administration. Vitamin B12 absorption is an active process that requires gastric intrinsic factor. Intrinsic factor is a glycoprotein secreted by the gastric mucosa. Passive diffusion through the intestinal wall can occur but large amounts of B12 are required (i.e. >1 mg). Following oral doses less than 3 mcg, peak plasma concentrations are not reached for 8 to 12 hours because the vitamin is transiently retained in the wall of the lower ileum. Vitamin B12 is rapidly absorbed from intramuscular (IM) and subcutaneous (SC) sites of injection; peak plasma concentrations are reached within 1 hour after IM injection.

Distribution: Vitamin B12 is distributed into the liver, bone marrow, and other tissues, including the placenta. At birth, the blood concentration of vitamin B12 imneonates is 3 to 5 times that of the mother. Total body stores of vitamin B12 in healthy individuals are estimated to range from 1 to 11 mg, with an average of 5 mg; 50 to 90% is stored in the liver. Vitamin B12 is believed to be converted to coenzyme form in the liver and is probably stored in tissues in this form.

Elimination: Following IM administration of 0.1 to 1 mg of cyanocobalamin, 50 to 90% of the dose may be excreted in urine by glomerular filtration within 48 hours, with the major portion

being excreted in the first 8 hours. Hydroxocobalamin is more highly protein bound and is retained in the body longer than cyanocobalamin; however, it is not more effective in normalizing the hematocrit.

Nicotinamide

Nicotinamide is efficiently absorbed from the gastrointestinal tract. At low doses, absorption is mediated via sodium-dependent facilitated diffusion. Passive diffusion is the principal mechanism of absorption at higher doses. Doses of up to three to four grams of nicotinamide are almost completely absorbed. Nicotinamide is transported via the portal circulation to the liver and via the systemic circulation to the various tissues of the body. Nicotinamide enters most cells by passive diffusion and enters erythrocytes by facilitated transport. Niacin and niacinamide are readily absorbed from the GI tract following oral administration, and niacinamide is readily absorbed from subcutaneous and IM injection sites. Nicotinamide is the primary circulating form of the vitamin. It is transported to tissues where nicotinamide adenine dinucleotide (NAD) is locally synthesised and used. Nicotinamide readily passes the blood-brain barrier and is taken up by the brain cells by a high-affinity transport system. In the rat, the liver mitochondrial fraction, pancreatic alpha-cells, erythrocytes and cells of the testis prefer nicotinamide as substrate for the synthesis of NAD(P). Liver and kidney cells prefer nicotinic acid as substrate. Brain cells have a high affinity for nicotinamide, but not for nicotinic acid. Nicotinamide is the main substance that is transported between the different tissues as a precursor of NAD synthesis. This can be deamidated to form nicotinic acid (and re-converted to NAD) or methylated and released via urine. Excretion of the amide (and its metabolites) tends to be more extensively compared to the acid.

In amounts needed for physiologic function as a coenzyme (12-18 mg daily), niacin is converted to niacinamide; larger doses of niacin are converted to niacinamide to only a minor degree. Niacinamide is metabolized in the liver to N-methylniacinamide, other N-methylated derivatives, and nicotinuric acid (the glycine conjugate of niacin). These metabolites are excreted in urine. Following administration of physiologic doses of niacin or niacinamide, only a small amount of niacinamide is excreted unchanged in urine; however, following administration of larger doses, a greater proportion of niacin and niacinamide is excreted unchanged.

D-Panthenol

D-Panthenol is soluble in water and alcohol, although insoluble in fats and oil based substances. With the appropriate vehicle, D-Panthenol is easily penetrated into the skin. Rate of penetration and absorption is reduced when D-Panthenol is administered as an oil/water formula. D-Panthenol is readily converted to pantothenic acid which is widely distributed into body tissues, mainly as coenzyme A. Highest concentrations are found in the liver, adrenal glands, heart, and kidneys. D-Panthenol is readily converted to pantothenic acid which is widely distributed into body tissues, mainly as coenzyme A. Highest concentrations are found in the liver, adrenal glands, heart, and kidneys. Milk of nursing mothers receiving a normal diet contains about 2 ug of pantothenic acid per mL. About 70% of an oral dose of pantothenic acid is excreted unchanged in urine and about 30% in feces.

CLINICAL EFFICACY

The B vitamins function as enzyme cofactors and coenzymes or their precursors. Deficiencies of vitamins are classified into two; either primary or secondary. Primary deficiency occurs when human/organism does not get sufficient vitamin from the diet. Secondary deficiency may be as a result of an underlying disorder which limits or prevents the absorption or use of vitamin, due to lifestyle factors, such as excessive alcohol consumption, smoking, or use of medications that interfere with absorption or use of vitamins.

Unless a coenzyme like B vitamins is present, enzymes essential for metabolic processes cannot function. Therefore, deficiencies of B-vitamins affect overall health and develop varied symptoms including tiredness and fatigue, breathlessness, headaches, dizziness, pale skin, anemia, lack of appetite and weight loss. Well-researched human deficiencies of B-vitamins involve niacin (pellagra), thiamine (beriberi), folate (neural tube defects). However, lack of vitamin B6 may also cause skin disorders, such as irritation or a rash. It can also lead to irritation, depression or increased risk of infections. Common symptoms of vitamin B12 deficiency, may be sore tongue, mouth ulcers, paraesthesia (known better as pins and needles), irritability and depression. Further symptoms in people with anaemia caused by a deficiency of folate can include numbness, muscle weakness and depression.

The treatment with thiamine shows significant increases in appetite, body weight, energy intake, general well-being, and decreased fatigue. Thiamine supplementation also tended to reduce daytime sleep durations, improve sleep patterns, and increase activity levels.

The most striking clinical signs of thiamine deficiency are related to the nervous system. Polyneuritis and paralysis of the peripheral nerves predominate. Manifestations are seen in the autonomic, the sensory, and the motor systems. In the sensory system tactile sensation is first affected, then there is pain, and finally temperature sensitivity is altered. There is increasing muscular weakness which is readily demonstrated by the inability of the individual to rise from a squatting position without assistance and, as the disease progresses, there is atrophy of the leg muscles. The tendon reflexes are also affected especially with loss of ankle and knee jerks. Painful calf muscles and, eventually, foot drop and, later, wrist drop may also develop. Thiamine deficiency is also associated with recurrent aphthous stomatitis.

Increased levels of homocysteine are considered biomarkers of cardiovascular diseases. A clinical study evaluated the effect of treatment with pyridoxine on plasma total homocysteine concentration in 20 women with clinical and biochemical deficiencies of pyridoxine. Result showed that plasma total homocysteine levels tended to be higher in women with clinical and biochemical deficiency of vitamin B6 and therapy with pyridoxine reduced its level significantly. The pyridoxine deficiency may be associated with the occurrence of oral lesions in anaemic patients.

The efficacy of cyanocobalamin treatment in patients having recurrent aphthous ulcers with normal or reduced serum vitamin B12 (cobalamin) levels was studied. A significant increase in cobalamin levels was observed after cyanocobalamin treatment. A significant decrease in aphthous ulcer frequency was also concurrently observed. 96% of the patients showed good response to replacement treatment.

The deficiency of vitamin B3 is characterized by hyperpigmentation and thickening of the skin, inflammation of the tongue and mouth, and digestive disturbances including indigestion, anorexia, and diarrhea, irritability, amnesia, and delirium. Nicotinamide shows anti-anxiety effect equivalent to a highly potent benzodiazepine in schizophrenics.

The pantethine form of vitamin B5 has been reported to have lipid-lowering effects, with supplementation capable of reducing cholesterol and triglyceride levels. While a study reported that 2 g/d of pantothenic acid for two weeks decreased blood lactate levels and decreased oxygen consumption during prolonged exercise at 75-percent VO2max in highly trained endurance runners. A double-blind study of persons with rheumatoid arthritis patients, who had not responded to previous drug treatment with salicylates, compared the addition of pantothenic acid (500 mg/d initially, increasing to 500 mg four times daily by the 10^{th} day) with placebo. A significant reduction in morning stiffness, degree of disability, and severity of pain was reported for persons taking pantothenic acid.

PRECLINICAL SAFETY DATA

Toxicity

Thiamine Hydrochloride

Toxicity Data: Oral LD50 (rat): 3710 mg/kg; Intraperitoneal LD50 (rat): 481 mg/kg; Subcutaneous LD50 (rat): 560 mg/kg; Oral LD50 (mouse): 8224 mg/kg; Intraperitoneal LD50 (mouse): 200 mg/kg; Subcutaneous LD50 (mouse): 266 mg/kg

Little information is published concerning thiamine tolerance and toxicity in domestic animal species. Studies in mice, rats, rabbits and dogs indicate that parenteral administration (80–400 mg/kg bw) of thiamine (hydrochloride) may be the only route by which signs of thiamine toxicity can be produced. In those animal species thiamine toxicity is characterised by depression of the respiratory centre; however, the mechanism of those effects is unknown. The NRC (1987) concluded that dietary intake of thiamine up to 1000 times the requirement level are apparently safe for most animal species.

Pyridoxine Hydrochloride

The use of supplemental Vit B6 has not been associated with toxicity, although the inactive form, pyridoxine, has been associated with reports of peripheral neuropathy. One hypothesis is that pyridoxine toxicity is caused by exceeding the liver's ability to phosphorylate pyridoxine to P5P, yielding high serum levels of pyridoxine which may be directly neurotoxic or may compete with P5P for binding sites, resulting in a relative deficiency. The electrophysiological and neurological examination of 17 homocystinuric patients who had been treated with 200-500 mg pyridoxine HCl daily for 10-24 years, and found no evidence of neuropathy. Most reported cases of neuropathy associated with pyridoxine supplementation have involved intake of at least 500mg/day for two years or more. While there is no doubt that vitamin B6 can be neurotoxic in gross excess, there is considerable controversy over the way in which toxicological data have been translated into advised limits.

Cyanocobalamin

Vitamin B12 has been considered of very low toxicity by several international bodies. According to the Scientific Committee on Food (SCF; EC, 2000), "no adverse effects have been associated with excess vitamin B12 intake from food or supplements in healthy individuals. Vitamin B12 has a history of safe long-term use as a therapeutic agent given in high dosages per oral, or via intramuscular injections, for treatment of disorders associated with impaired vitamin B12 absorption, such as in gastrectomy and malabsorption. In vitamin B12 replacement therapy oral or intramuscular dosages between 1,000–5,000 µg vitamin B12 are used, with no supportive evidence of adverse effects up to at least 5 years. Recently, the US Food and Drug Administration (FDA, 2014) came to similar conclusions as the SCF: "Vitamin B12 has shown no toxicity to animals at several thousand times their nutritional requirements. In man, pernicious anaemia patients have received daily doses for years 10 to 20 times that of the highest estimate of average daily consumption. The only reaction to vitamin B12 so far demonstrated in man is the development of sensitivity that can become manifest as allergy or anaphylaxis after parenteral administration of relatively high doses".

Nicotinamide

The SCF (EC, 2002) carried out a comprehensive overview of the toxicological profile of nicotinic acid and nicotinamide including data and effects in humans and animals. The data include a number of studies in laboratory animals and humans. High doses of nicotinamide in rats caused hepatotoxicity. Genotoxicity tests on nicotinic acid and nicotinamide gave negative results. Most of these studies in humans considered the known vasodilatory effects, gastrointestinal effects, hepatotoxicity and glucose intolerance. A 4-week rat feeding study with nicotinamide showed increased liver weight, centrilobular hepatocellular hypertrophy with (in females) extramedullary haematopoiesis in the spleen at 1 000 mg/kg bw per day with a NOAEL of 215 mg/kg bw per day (OECD SIDS, 2002).

D-Panthenol

According to Regulation (EC) No 429/2008, tolerance, metabolism and residue, and toxicological (with concern to consumer safety) studies are not required for vitamins, pro-vitamins and chemically defined substances having similar effects which are already authorised as feed additives under Directive 70/524/EEC and which do not have the potential to accumulate, which the FEEDAP Panel considers is the case for pantothenic acid.
Acute oral LD50 values for pantothenic acid are 10,000 mg/kg in mice and rats, with lethal doses producing death by respiratory failure. Chronic administration for 6 months produced no toxic signs, weight loss, or histopathological changes in rats (dose up to 2,000 mg/kg, dogs (50 mg/kg), and monkeys (200-250 mg/kg).

Carcinogenicity and genotoxicity

Thiamine Hydrochloride: Not found to be a potential carcinogen and in the International Agency for Research on Cancer (IARC) Monographs, Volumes 1-112. No teratogenic effects reported.

Pyridoxine Hydrochloride: There is no evidence from the long-term use of large doses of pyridoxine that this compound is carcinogenic.

Cyanocobalamin: There is no evidence from the long-term use in patients with pernicious anaemia that this compound is carcinogenic (FDA, 2014). No studies have investigated the reproductive or developmental toxicity of vitamin B12. In humans, the acute toxicity seems very low.

Nicotinamide: There were no reliable multigeneration studies of reproductive toxicity, but a rat developmental study on nicotinic acid showed no teratogenicity at 1000 mg/kg bw per day and a NOAEL (no observable adverse effect level) for maternal toxicity and fetotoxicity of 200 mg/kg bw per day (OECD SIDS, 2002).

D-Panthenol: Neither teratogenic nor fetotoxic effects were noted in the offspring when rats were fed calcium pantothenate before mating and throughout gestation

CLINICAL PARTICULARS

Contraindications:

Polybion A Injection is contraindicated in children below the age of 14 years.

Polybion A Injection is contraindicated in patients with known hypersensitivity to either of the active substances or any of the excipients. Polybion A Injection is also contraindicated in patients with cobalt hypersensitivity as Cyanocobalamin contains cobalt.

Special warnings and precautions for use:

The clinical picture as well as the laboratory parameters of funicular myelosis or of pernicious anaemia can lose specificity by administration of vitamin B12. Patients who have early Leber's disease (hereditary optic nerve atrophy) have been found to suffer severe and swift optic atrophy when treated with vitamin B12.

The intradermal test dose is recommended before vitamin B_{12} is administered to patients known to be sensitive to cobalamins. Parenteral administration of cyanocobalamin is the required treatment for originally diagnosed and relapsed pernicious anemia with severe neurologic manifestations. Also, in treatment of megaloblastic anemia associated with sprue, supplementation with folic acid is usually necessary and parenteral vitamin B_{12} may be required.

Vitamin B12 (cyanocobalamin) may improve folate-deficient megaloblastic anemia. Use of the product may improve this condition due to the presence of vitamin B12 (cyanocobalamin) and care should be taken that a correct diagnosis is not masked

Serum potassium concentrations should be monitored during early vitamin B_{12} therapy and potassium administered if necessary, since fatal hypokalemia could occur upon conversion of megaloblastic anemia to normal erythropoiesis with vitamin B_{12} as a result of increased erythrocyte potassium requirements. Therapeutic response to vitamin B_{12} may be impaired by concurrent injection, uremia, concomitant treatment with chloramphenicol or misdiagnosis.

If symptoms of peripheral sensory neuropathy (paraesthesia) occur, the dosage should be reviewed and treatment with the medicinal product discontinued, if necessary. Neuropathies have been observed under long-term intake (over 6-12 months) of daily dosages exceeding 50 mg vitamin B6 as well as in short-term intake (over 2 months) of more than 1 g vitamin B6 per day. Therefore, regular monitoring is recommended under long-term treatment.

Routine testing for hypersensitivity, in many cases, may not detect hypersensitivity. Nevertheless, a skin test should be performed on patients who are suspected of drug allergies or previous reactions to thiamine, and any positive responders should not receive thiamine by injection.

Do not re-use syringes and needles. Syringes and needles must be disposed immediately after use. Used syringes and needles must not be disposed in waste bins or toilets, but they must be disposed in a special sharps container.

Interaction with other medicinal products and other forms of interaction:

Thiamine Hydrochloride: Thiamine is inactivated by 5-fluorouracil as the latter competitively inhibits the phosphorylation of thiamine to thiamine pyrophosphate. Antacids diminish the absorption of thiamine. Loop diuretics, e.g. furosemide that inhibit tubular reabsorption may cause increased excretion of thiamine in long-term therapy and, thus, lowering of the thiamine serum level. Beverages containing sulphite (e.g. wine) enhance thiamine degradation. Alcohol and black tea diminish the absorption of thiamine.

Pyridoxine hydrochloride: The antituberculosis drug isoniazid can result in a functional vitamin B6 deficiency. Anti-parkinsonian drugs benserazide and carbidopa cause vitamin B6 depletion by forming hydrazones. Pyridoxine will reduce the efficacy of levodopa in controlling parkinsonian symptoms, the magnitude of the effect proportional to the dose of pyridoxine. There have been many reports of abnormal tryptophan metabolism in women taking either oral contraceptive or menopausal hormone replacement therapy, which have been interpreted as indicating oestrogen-induced vitamin B6 deficiency or depletion.
The simultaneous administration of pyridoxine antagonists [e.g. isoniazide (INH), hydralazine, D penicillamine or cycloserine] may decrease the efficacy of vitamin B6 (pyridoxine).

Cyanocobalamin: Most antibiotics, methotrexate and pyrimethamine invalidate folic acid and vitamin B 12 diagnostic microbiological blood assays. Chloramphenicol may antagonize the hematopoietic response to vitamin B12. Hematopoietic response in such patients should be monitored. Colchicine, aminoglycosides, certain anticonvulsants (e.g., phenytoin, Phenobarbital, primidone), para-aminosalicylic acid or excessive alcohol intake for longer than 2 weeks may impair the absorption of vitamin B12. Vitamin C may destroy vitamin B12. Patients should avoid ingesting large amounts of vitamin C within 1 hour of oral vitamin B12 administration. Histamine2-Receptor Antagonists (cimetidine, ranitidine, nizatidine, famotidine) may potentially cause vitamin B12 deficiency by decreasing gastric acid cleavage of vitamin B12 from food sources. This may be important in patients with low stores of vitamin B12 or in patients taking H2-antagonists for extended periods of time (>2 years).

Nicotinamide: Concomitant use of niacinamide and antiepileptic drugs, specifically carbamazepine, diazepam, and sodium valproate, apparently potentiates the anticonvulsant action of these drugs. In addition, niacinamide may decrease clearance of carbamazepine when used simultaneously.

D-Panthenol: Ascorbic acid appears to have a pantothenic acid-sparing effect in rats. Animal experiments suggest that pantothenic acid might help prevent some side effects of valproic acid (VPA). *In utero* exposure to VPA during pregnancy is associated with an increased risk of neural tube defects (NTDs) in animals. Animal research on adrenal function suggests that pantothenic acid supplementation might augment the response to corticosteroids. A study reported that pantothenic acid levels were significantly lower in females using oral contraceptives compared with females who were not. Pantothenic acid has been reported to have no estrogenic action itself, but enhanced the action of estradiol in rats. Experimental work from the 1950s suggested that pantothenic acid might interfere with the ability of some antibiotics – aureomycin, erythromycin, and streptomycin to inhibit the growth of certain microorganisms under *in vitro* conditions.

Pregnancy and Lactation:

The safety of B-vitamins in pregnancy and lactation has not been fully established. B-group vitamins are secreted into human breast milk, but risks of overdose for the infant are not known. This product should only be used in pregnancy or lactation period only if potential benefit outweighs the risks. Extreme precautions and regular follow-up is recommended if the product is used during these phases.

Thiamine Hydrochloride: Studies in pregnant women have not shown that thiamine hydrochloride 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, thiamine hydrochloride should be used during pregnancy only if clearly needed. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when thiamine hydrochloride is administered to a nursing mother.

Pyridoxine hydrochloride: Vitamin B6 is excreted into breast milk. In individual cases, high doses of vitamin B6, ie >600mg daily, may inhibit the production of breast milk. While some have expressed concern over the inhibition of breast milk secretion by pyridoxine, most other experts have cautioned that pyridoxine deficiency may cause seizures in the neonate. The American Academy of Pediatrics considers the use of pyridoxine to be usually compatible with breast feeding.

Cyanocobalamin: No adverse effects have been reported with ingestion of normal daily requirements during pregnancy. Vitamin B12 is distributed into the milk of nursing women in concentrations that approximate the maternal blood vitamin B12 concentration. No adverse effects have been reported with intake of normal daily requirements during lactation. The American Academy of Pediatrics considers its use to be usually compatible with breast feeding.

Nicotinamide: A study observed an association between niacinamide deficiency and pregnancy-induced hypertension (PIH). Niacinamide is actively transported to the fetus. Higher concentrations are found in the fetus and newborn, rather than in the mother. Niacin, the precursor to niacinamide, is actively excreted into breast milk. Reports on the excretion of niacinamide in milk have not been located, but it is probable that it also is actively transferred. The National Academy of Sciences' RDA for niacin during lactation 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 for those patients with inadequate nutritional intake.

D-Panthenol: Pantothenic acid has an FDA Pregnancy category A rating for doses at or below the DRI level. The well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters) for doses at or below the DRI level. Pantothenic acid has a Pregnancy category C rating when dosed above the DRI (i.e., animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks).

Effects on ability to drive and use of machines:

No specific instructions or precautionary measures are intended for driving the vehicle or working on a machine, when a person is being administered the course of Polybion A injection.

Undesirable effects:

Immune system disorders: frequency not known: Hypersensitivity reactions, such as sweating, tachycardia, and skin reactions with itching and urticaria. Very rare: Anaphylactic shock
Gastrointestinal disorders: frequency not known: Gastrointestinal complaints, such as nausea, vomiting, diarrhoea and abdominal pain.
Skin and subcutaneous tissue disorders: frequency not known: Isolated cases of acne or eczema have been reported after high parenteral doses of vitamin B12
General disorders and administration site conditions: frequency not known: Injection site reactions such as injection site pain.
Renal and urinary disorders: frequency not known: Chromaturia ('reddish urine') appeared during the first 8 hours after an administration and typically resolves within 48 hours.

Apart from the undesirable effects mentioned above, the following effects may be seen based on individual active ingredient:
Thiamine Hydrochloride: An occasional individual may develop a hypersensitivity or life threatening anaphylactic reaction to thiamine, especially after repeated injection. Collapse and death have been reported. A feeling of warmth, pruritus, urticaria, weakness, sweating, nausea, restlessness, tightness of the throat, angioneurotic edema, cyanosis, pulmonary edema, and hemorrhage into the gastrointestinal tract have also been reported. Some tenderness and induration may follow IM use.
Pyridoxine hydrochloride: Severe sensory neuropathy has been described in patients receiving large doses of pyridoxine (2 to 6 g daily) for periods of 2 to 40 months. There has, however, been debate as to whether smaller doses can produce such effects.
Cyanocobalamin: Vitamin B_{12} is usually non-toxic even in large doses. However, mild, transient diarrhea, polycythemia vera, peripheral vascular thrombosis, itching, transitory exanthema, feeling of swelling of entire body, pulmonary edema and congestive heart failure early in treatment, anaphylactic shock and death have been reported following vitamin B_{12} administration.
Nicotinamide: Data on the side effects of niacinamide and niacin are often confused as earlier studies used mixtures of the two in preparations. Furthermore, the purity of niacinamide preparations varies considerably as some preparations include trace amounts of niacin. Older

clinical studies report relatively frequent liver enzyme abnormalities; however, recent studies using purified niacinamide have not detected such abnormalities. Nausea is usually the first side effect noted with niacinamide.
D-Panthenol: The most commonly reported side effect is mild transient gastrointestinal disturbance such as nausea, heartburn, and diarrhea. Adverse effects typically do not occur until doses exceed 1 gram daily.

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 requested to report any suspected adverse reactions immediately.

Overdose:

Thiamine Hydrochloride: Parenteral doses of 100 mg to 500 mg singly have been administered without toxic effects. However, dosages exceeding 30 mg 3 times a day are not utilized effectively. When the body tissues are saturated with thiamine, it is excreted in the urine as pyrimidine. As the intake of thiamine is further increased, it appears unchanged in the urine. Thiamine has a broad therapeutic range. Very high doses (over 10 g) have a ganglion-blocking effect, similar to that of curare, and suppress the conduction of nerve impulses

Pyridoxine hydrochloride: There are no known toxicities associated with vitamin B6 in lower doses. However, vitamin B6 can be neurotoxic when taken in large doses. Several cases have been reported in people taking 2 grams or more per day. Symptoms included tingling in the hands and feet, decreased muscle coordination, and a stumbling gait. Long-term intake (> 6-12 months) of a daily dosage > 50 mg vitamin B6 may, however, cause peripheral sensory neuropathy and other sensorial neuropathy syndromes. These symptoms improve gradually upon vitamin discontinuation. Neuropathies with ataxia and sensitivity disorders, cerebral convulsions with EEG changes as well as, in individual cases, hypochromic anaemia and seborrhoeic dermatitis have been described after administration of more than 2 g daily.

Cyanocobalamin: Allergic reactions, eczematous skin changes and a benign form of acne have been observed after high parenteral doses (in rare cases also after oral doses).

Nicotinamide: The high-dose niacinamide include heartburn, vomiting, flatulence, and diarrhea. Mild headaches and dizziness have been reported after giving niacinamide parenterally.

D-Panthenol: Acute oral LD50 values for pantothenic acid are 10,000 mg/kg in mice and rats, with lethal doses producing death by respiratory failure. Chronic administration for 6 months produced no toxic signs, weight loss, or histopathological changes in animals.

Treatment of overdose consists of discontinuation of the product and other measures as clinically indicated

PHARMACEUTICAL PARTICULARS:

Shelf life: 18 months

Special precautions for storage: Store below 30^0C. Protect from light.
Keep out of reach of children.
Pack : 2 ml. ampoule

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