PRODUCT LITERATURE

TRIOBION TABLET
Each tablet contains

Thiamine Mononitrate	100 mg
Pyridoxine HCI	50 mg
Cyanocobalamin	100 mcg

Product description
Round, pink coloured, sugar coated tablet.

Pharmacodynamics properties
Triobion tablets contain a combination of neurotropic active substances of the vitamin B complex. The vitamins thiamine (B1), pyridoxine (B6) and cobalamin (B12) contained play a particular role as coenzymes in the intermediary metabolism of the central and peripheral nervous system.
Like all other vitamins, they are essential nutrients which the body cannot synthesise itself.
Therapeutic supply of vitamins B1, B6 and B12 may supplement inadequate nutritive vitamin intake and thus ensure the availability of the required quantities of coenzymes.
The therapeutic use of these vitamins in diseases of the nervous system serves, on the one hand, to compensate for concomitant deficiencies (possibly due to an increased requirement induced by the disease) and, on the other, to stimulate natural repair mechanisms.

Thiamine (vitamin B1):
Thiamine pyrophosphate (TPP) is the effective form of vitamin B1 and acts as a coenzyme for a number of enzymes (e.g. pyruvate dehydrogenase and transketolase). Accordingly, vitamin B1 is primarily involved in the carbohydrate metabolism; however, it also intervenes in the synthesis of lipids and amino acids. Nerve cells cover their energy requirement exclusively via enzymatic oxidation and decarboxylation of glucose, so that an adequate supply of vitamin B1 is of crucial importance. Thiamine is also involved in the conduction of nerve impulses.
Models used in animal studies have indicated analgetic activity for vitamin B1.
Manifestations of vitamin B1 deficiency are very multifaceted and can involve central and peripheral nervous system, the cardiovascular system, skin and other body systems. Specific symptoms can include polyneuropathy with paraesthesia (tingling, burning, numbness), hyperesthesia (increased sensitivity), muscle weakness, altered temperature sensitivity, oedema, and others.

Pyridoxine (vitamin B6):
Pyridoxal phosphate, the biologically active form of pyridoxine, is the determinative coenzyme in amino acid metabolism. It is involved in the formation of physiologically active amines (e.g. serotonin, histamine, adrenalin) through decarboxylation processes, as well as in anabolic and catabolic processes through transamination.
Pyridoxal phosphate plays an essential role in the nervous system, especially in the enzymatically controlled neurotransmitter metabolism. As a catalyst of the first biosynthesis steps of sphingosine, pyridoxal phosphate also has a key role in the metabolism of sphingolipids. Sphingolipids are essential constituents of the myelin sheaths of nerve cells. Animal experimental models have demonstrated that vitamin B6 has an analgesic effect.
Vitamin B6 deficiency can be associated with peripheral neuritis and neuropathy, paresthesia, burning, painful dysesthesia, disorders of oxalate metabolism, depression of immune responses, anemia, lesions of the mucous membranes and other symptoms.

Cobalamin (vitamin B12):
Vitamin B12 in its coenzyme forms (5-deoxyadenosyl cobalamin and methyl cobalamin) is involved in enzymatically catalysed intramolecular hydrogen displacements and in intramolecular transfers of methyl groups. Vitamin B12 is also involved in methionine synthesis (closely coupled to the synthesis of nucleic acids) and in lipid metabolism, via the conversion of propionic acid into succinic acid.
Vitamin B12 is involved in the methylation of the myelin basic protein, a constituent of the myelin sheaths of the nervous system. Methylation increases the lipophilic properties of the myelin basic protein, which favours increased integration in the myelin sheaths.
Vitamin B12 deficiency can result in neurological symptoms like paresthesia, numbness, gait impairment, impaired vibration sense, polyneuritis (particularly sensory, in the distal extremities), ataxia and others. Further symptoms can be anaemia, optic atrophy, altered mental status and others.

Combination of vitamins B1, B6 and B12:
Neurotropic vitamins B1, B6 and B12 alone, and in combination as the result of biochemical synergy, have special significance for the metabolism of the nervous system, which justifies their combined use.
Further, in most of the patient populations such as elderly, diabetic patients and others, deficiency of all three neurotropic vitamins is present.
Animal studies have shown that this combination of neurotropic B vitamins accelerates regenerative processes in damaged nerve fibres, which finally leads to enhanced restoration of function and muscle innervation. In the model of experimental diabetes in rats, administration of B complex vitamins prevented or attenuated the characteristic nerve damage, so that deterioration of the functional properties was counteracted (antineuropathic effect).
Further, the combination of B1, B6 and B12 has been proven to have a synergistic effect when combined with NSAIDs in the treatment of pain.

Pharmacokinetics properties
Combined administration of vitamins B1, B6 and B12 is not expected to have a negative effect on the pharmacokinetics of the individual vitamins.

Thiamine(vitamin B1) :
Has after oral administration a dose-dependent dual transport mechanism:
Active absorption up to concentrations of 2 µmol and passive diffusion in concentrations over 2 µmol.
There is almost no absorption in the stomach and in distal segments of the small intestine. Thiamine formed by the large intestinal flora is not absorbed. Absorption of thiamine takes place after phosphorylation in the epithelial cells; a carrier mechanism is assumed to be involved in the passage through the intestinal wall.
After absorption by the intestinal mucosa, thiamine is transported to the liver via the portal circulation. In the liver, thiamine is phosphorylated to thiamine pyrophosphate (TPP) and thiamine triphosphate (TTP) by means of thiamine kinase.
The biological half-life of thiamine in humans is about 9.5 to 18.5 days, with an elimination half-life is approx. 4 hours.
The human body can store approx. 30 mg thiamine. On account of the rapid metabolisation, the reserve capacity, at 4-10 days, is very limited.

Pyridoxine(vitamin B6):
Pyridoxine is absorbed very rapidly, mainly in the upper gastrointestinal tract, and is excreted with a maximum between 2 and 5 hours.
Vitamins are bound to albumin. Vitamin B6 passes into the spinal fluid, is secreted into breast milk, and permeates the placenta. The principal excretion product is 4-pyridoxic acid; the amount of the latter depending on the vitamin B6 dose taken up.
Vitamin B6 is phosphorylated mainly in the liver, forming the biologically active pyridoxal phosphate. To cross cell membranes, phosphorylated vitamin B6 must be hydrolysed by alkaline phosphatase to free vitamin B6. Transport into the cells is by simple diffusion followed by rephosphorylation, and a specialized intestinal carrier-mediated system for pyridoxine uptake has been discussed recently. Peak concentrations are reached after 3.5 to 4 hours. The biological half-life of pyridoxal phosphate is about 15 - 25 days. The storage capacity for vitamin B6 is 14 to 42 days.
Approx. 40 to 150 mg can be stored, 1.7 to 3.6 mg is excreted in the urine per day.

Cobalamin (vitamin B12):
Cobalamin is absorbed from the gastrointestinal tract by means of 2 mechanisms:
- release through gastric acid and immediate binding to the intrinsic factor. A maximum of 1.5-2 µg of oral vitamin B12 is absorbed via this mechanism
- independently of the intrinsic factor through passive influx in the blood

At doses over 1.5 µg the latter mechanism increases in significance.
Patients with pernicious anaemia absorb approx. 1% of oral doses of 100 µg and over.
Vitamin B12 is stored predominantly in the liver, the daily requirement is 1 µg.
The turnover rate is 2.5 µg B12 per day, or 0.05% of the stored quantity. The biological half-life is about 1 year.
Vitamin B12 is mainly secreted into bile and largely reabsorbed during the enterohepatic circulation.

Indication
For the prevention and treatment of deficiencies of Vitamins B1, B6, B12.

Recommended dose
Adult: 1 tablet, 2 or 3 times a day

Route of administration
Oral

Contraindication
Risk-benefit should be considered when the following medical problems exist:
- Sensitivity to thiamine
- Wernicke's encephalopathy (intravenous glucose loading may precipitate or worsen this condition in thiamine-deficient patients; thiamine should be administered prior to glucose)
- Sensitivity to pyridoxine
- Sensitivity to cyanocobalamin or hydroxocobalamin

Except under special circumstances, this medication should not be used when the following medical problem exists:
- For cyanocobalamin:
  - Leber's disease (optic nerve atrophy has occurred rapidly after administration; cyanocobalamin concentrations are already elevated)

Warnings and precautions
- Pediatrics
  Problems in paediatrics have not been documented with intake of normal daily recommended amounts.
- Geriatrics
  Problems in geriatrics have not been documented with intake of normal daily recommended amounts. Studies have shown that the elderly may have impaired thiamine status, thereby requiring thiamine supplementation.
- Cross-sensitivity and/or related problems
  Individuals sensitive to other cobalamins (found naturally in foods) may be sensitive to vitamin B also.

Interaction with other medicaments
Note: Combinations containing any of the following medications, depending on the amount present, may also interact with pyridoxine.

Cycloserine, Ethionamide, Hydralazine or Immunosuppressants, such as:
Azathioprine, Chlorambucil,
Corticosteroids, Corticotropin (ACTH),
Cyclophosphamide, Cyclosporine Mercaptopurine,
Isoniazid or Penicillamine (may cause anemia or peripheral neuritis by acting as pyridoxine antagonists or increasing renal excretion of pyridoxine; recommended intakes for pyridoxine may be increased in patients receiving these medications)
- Estrogens or Contraceptives, estrogen-containing, oral (may increase recommended intakes for pyridoxine)
- Levodopa (concurrent use with pyridoxine is not recommended since levodopa's antiparkinsonian effects are reversed by as little as 5 mg of pyridoxine orally; this problem does not occur with the carbidopa-levodopa combination)

Note: Combinations containing any of the following, depending on the amount present, may also interact with vitamin B_{12} supplements,
- Alcohol, excessive intake for longer than 2 weeks Aminosalicylates or Colchicine, especially in combination with aminoglycosides (may act to reduce absorption of vitamin B_{12} from the gastrointestinal tract; requirements for vitamin B_{12} may be increased in patients receiving these medications)
- Antibiotics (may interfere with the microbiologic method of assay for serum and erythrocyte vitamin B_{12} concentrations and cause falsely low results)
- Folic acid (large and continuous doses may reduce vitamin B_{12} concentrations in blood)

Pregnancy and Lactation
Pregnancy/Reproduction
- Pregnancy; Thiamine
  Problems in humans have not been documented with intake of normal daily recommended amounts.
- Pregnancy; Pyridoxine
  Problems in humans have not been documented with intake of normal daily recommended amounts. However, exposure to large doses of pyridoxine in utero may result in a pyridoxine dependency syndrome in the neonate.

Breast-feeding
- Pyridoxine and Thiamine: Problems in humans have not been documented with intake of normal daily recommended amounts.
- Vitamin B_{12} is distributed into breast milk; however, problems in humans have not been documented with intake of normal daily recommended amounts.

Side effect
Those indicating need for medical attention
- Incidence rare
  - Anaphylactic reaction (coughing; difficulty in swallowing; hives; itching of skin; swelling of face, lips, or eyelids; wheezing or difficulty in breathing); usually after a large intravenous dose
  - Doses of 200 mg per day for over 30 days have been reported to produce a pyridoxine dependency syndrome.
  - High doses of pyridoxine (2 to 6 grams per day) taken for several months have caused a severe sensory neuropathy, progressing from unstable gait and numb feet to numbness and clumsiness of hands. This condition seems to be reversible on withdrawal of pyridoxine, although some residual weakness has been observed.

Those indicating need for medical attention

- Incidence rare
  - Anaphylactic reaction (skin rash; itching; wheezing); after parenteral administration

Those indicating need for medical attention only if they continue or are bothersome

- Incidence less frequent
  - Diarrhea,
  - itching of skin

Symptoms and Treatment of overdose
None

Storage Condition
Store below 30^{o}C, in a dry place, protected from direct light.
Keep away from reach of children
Jauhkan daripada kanak-kanak

Packing
Packed in plastic container of 30's and 100's tablet

Shelf life
2 years from date of manufacture

Name and Address of Manufacturer:
TERAPUTICS SDN. BHD. (590500-W)
Lot 10 & 11, PERDA Industrial Park,
Lorong IKS Simpang Ampat B,
14100 Simpang Ampat, S.P.S.,
Pulau Pinang, Malaysia

Name and Address of Product Registration Holder/ Distributor:
ZONTRON PHARMACEUTICALS SDN.BHD.
(445695-T)
Lot 10 & 11, PERDA Industrial Park,
Lorong IKS Simpang Ampat B,
14100 Simpang Ampat, S.P.S.,
Pulau Pinang, Malaysia

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