SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

TRIBEMINE Tablets

2. Qualitative and quantitative composition

Pyridoxine (Vitamin B6) Hydrochloride 250mg

Thiamine (Vitamin B1) Hydrochloride 100mg

Cyanocobalamin (Vitamin B12) 0.25mg

3. Pharmaceutical form

Tablets

4. Clinical particulars

4.1 Therapeutic indications

For the treatment of neurologic pain and metabolic disorders.

Vitamin B supplement.

Not intended for children below age 6.

4.2 Posology and method of administration

The recommended dose is usually 1-2 tablets per day.

To be taken with water.

If required, the tablets can be crushed and swallowed immediately.

If you forgot to take the medicine, do not take a double dose to make up for a forgotten dose.

4.3 Contraindications

Do not use the medicine if:

-There is a known allergy to one of the ingredients.

-You suffer from Laber's disease (hereditary disease that causes vision loss -atrophy of the sight nerve)

-In case of Amblyopia (lazy eye) in smoking people.

4.4 Special warnings and precautions for use

Do not use the medicine too often or for a long period without consulting a doctor.

If you are sensitive to a certain food or a certain medicine, you must inform the doctor before taking the medicine.

Using higher doses may damage the nervous system.

You should not take a higher dose than recommended or for a longer period than recommended- In your case, regular monitoring by your doctor is recommended since cases of neuropathies have been observed after the intake of high and continuous daily doses vitamin B6.

If you suffer from a blood disease, such as anemia, your doctor should check its cause before taking vitamin B12.

There have been cases of pyridoxine dependence and withdrawal when taking doses of pyridoxine (vitamin B6) for a month even lower than that contained in this medicine.

A possible adverse event caused by Vitamin B6 (Pyridoxine) is peripheral neuropathy, identified by symptoms like paraesthesia, stinging and burning sensation, usually in hands and feet.

Taking high dosage or after long term usage of products containing Vitamin B6, the risk for this adverse event increases, if you experience symptoms like- paraesthesia, stinging and burning sensation, you should stop treatment and refer to a doctor.

You should avoid exposure to the sun and ultraviolet rays, due to a possible risk of photosensitivity (with the appearance of skin lesions such as rash or blisters).

If you have previously had an allergy to vitamin B1 from contact with your skin (contact dermatitis) for occupational reasons, you may experience a relapse when taking this medicine.

<u>Interference with analytical tests</u>

If you are going to have any medical and diagnostic tests (including blood tests, urine tests, skin tests using allergens, etc.), tell your doctor that you are taking this medicine, as it may alter the

results. In some determinations of urobilinogen, theophylline, uric acid, or antibodies against intrinsic factor (IF), false results could be produced.

4.5 Interaction with other medicinal products and other forms of interaction

This medication may interact with the following medications:

Levodopa (for Parkinson's disease)

Phenobarbital, phenytoin (to treat epilepsy).

Altretamine and 5-fluorouracil (for some types of cancers).

Amiodarone (for the heart).

Neuromuscular blocking drugs (used in anesthesia, for surgery).

Several drugs can interfere with pyridoxine (vitamin B6) and can reduce its levels, including:

antibiotics to cure tuberculosis (isoniazid, cycloserine, ethionamide and pyrazinamide),

penicillamine (for rheumatic diseases),

hydralazine (for blood pressure),

immunosuppressants such as corticosteroids,

cyclosporine (used in organ transplants, among other diseases).

Several medications can decrease the absorption of vitamin B12 or reduce its effect, such as:

ascorbic acid in large doses,

antibiotics such as neomycin and chloramphenicol,

colchicine (for the treatment of gout),

h3 antagonists (medicines against heartburn or ulcer of the stomach),

amino salicylic acid in long courses (for intestinal disease),

omeprazole (for stomach ulcer),

medicines for epilepsy,

metformin (for diabetes),

folic acid in high doses.

Oral contraceptive can reduce the levels of vitamins B6 and B12.

Isoniazid -Because of B6

<u>Alcohol:</u>

Excessive alcohol intake reduces the absorption of vitamins.

4.6 Pregnancy and lactation

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor before using this medicine.

It is not recommended in women of childbearing potential not using effective contraception.

4.7 Effects on ability to drive and use machines

There are no known effects of the product on the ability to drive or use machines. However, this medicine may cause drowsiness in a few patients, who should not drive and/or use dangerous machines during treatment.

4.8 Undesirable effects

Stop taking the medicine and refer to a doctor in the following situations:

If you experience symptoms like paraesthesia, stinging and burning sensation (peripheral neuropathy).

Skin rash or irritation.

Like all medicines, this medicine can cause side effects, although not everybody gets them.

-Infrequently the following may appear:

nausea, vomiting, headache, drowsiness, paraesthesia (tingling sensation in the arms and legs) and skin rash (redness or swelling).

Hypersensitivity reactions (allergic reactions) to vitamin B1, B6 and B12 have also been reported.

-Other side effects that have been reported, often not exactly known, are:

Digestive discomfort, diarrhea, loss of appetite with high doses, photosensitivity with skin lesions such as blisters, redness, itching, very occasionally reduction in the number of platelets (thrombocytopenia), insomnia, disorder with reduced sensation and tingling, among other symptoms, which generally subside when treatment is stopped, worsening of Leber's disease (an inherited disease that causes vision loss), changes in the color of urine, which usually disappears within 48 hours, occasionally anaphylactic reaction with itching, sweating, shortness of breath, increased heartbeat, etc.

Reporting side effects

Side effects can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment" found on the Ministry of Health homepage (www.health.gov.il) that directs

you to the online form for reporting side effects, or by entering the link:
https://sideeffects.health.gov.il

4.9 Overdose

If you have taken more than you should, you may experience symptoms such as: gastrointestinal discomfort (diarrhoea, nausea, vomiting) and headache.

Due to the pyridoxine content, you should suffer from nervous disorders such as altered or reduced sensitivity, tingling, numbness in the feet and hands, unstable gait, etc., sensitization to sunlight with skin rashes may also appear, drowsiness, lethargy, respiratory distress, among other effects, depending on the dose, increase in the serum concentration of AST (SGOT) (a transaminase) and decrease in serum concentrations of folic acid.

In rare cases, a severe allergic reaction (anaphylactic shock) may occur.

In children:

Accidental ingestion of very high doses of vitamin B6 can also cause sedation, weakness, and respiratory distress.

In case of overdose or accidental ingestion, immediately consult your doctor or pharmacist, or go to a medical center.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vitamin B1 in combination with vitamin B6 and/or vitamin B12, ATC code: A11DB.

Vitamin deficiency may be the result of an inadequate diet, perhaps due to increased requirements, or it may be a consequence of illness, excessive alcohol intake or medication.

Tribemin is an association of water-soluble vitamins B1, B6 and B12 ; these vitamins act as cofactors of specific enzymes and at pharmacological doses are used for the treatment of deficiency states and the symptoms that manifest themselves.

Thiamine combines with adenosine triphosphate (ATP) to form thiamine pyrophosphate (TPP), the active form, a coenzyme necessary for carbohydrate metabolism, especially in nerve cells. Thiamine plays an important role in the decarboxylation of alpha-keto acids. Thiamine deficiency can affect, among others, the peripheral nervous system, gastrointestinal tract and cardiovascular system; a manifestation of severe deficiency is beriberi. Thiamine requirements

may be increased in the following situations: alcoholism, chronic fever, prolonged infections, persistent diarrhea, etc.

Pyridoxine and two related compounds, pyridoxal and pyridoxamine, are known as Vitamin B6. These compounds are metabolically and functionally interrelated; in the liver they are mainly transformed into pyridoxal phosphate, the active form, and to a lesser

extent they are converted to pyridoxamine phosphate, also active; pyridoxine hydrochloride is the most widely used preparation clinically.

Pyridoxal phosphate acts as a coenzyme in the metabolism of proteins, carbohydrates and fats. Metabolic transformations of proteins and amino acids include transamination, decarboxylation, desulfurization, synthesis and racemization; pyridoxal phosphate is involved in the metabolism of tryptophan to niacin and in the conversion of methionine to cysteine; it also has a role as a cofactor for glycogen phosphorylase, polyunsaturated fatty acids and phospholipids; it also appears to be a modulator of the actions of steroid hormones.

Pyridoxal phosphate plays an essential role in the nervous system, it is involved in the metabolism of brain amines (serotonin, norepinephrine, dopamine), neurotransmitters controlled by enzymes. As a catalyst of the first stages of sphingosine biosynthesis, it also plays a key role in the metabolism of sphingolipids, which are essential constituents of the myelin sheaths of nerve cells.

Vitamin B6 deficiency may be associated with peripheral neuropathy, paresthesia, burning, painful dysesthesia, depression, irritability, anemia, lesions of mucous membranes, and other symptoms.

Cyanocobalamin is a form of vitamin B12 (cobalamin), a generic term that encompasses several compounds called cobalamins that contain cobalt as the central atom in a macrocyclic tetrapyrrole group (corrin ring) linked to a dimethyl benzimidazolyl nucleotide. Cobalt can be linked to various groups, such as cyano, deoxyadenosyl, methyl or hydroxyl, forming cyanocobalamin, deoxyadenosylcobalamin, methylcobalamin or hydroxocobalamin, respectively. In the body, vitamin B12 is mainly found in plasma as methylcobalamin (mecobalamin) and as adenosylcobalamin (cobamamide), which act as coenzymes.

Both vitamin B12 and folate are required for the synthesis of purine nucleotides and the metabolism of some amino acids; both are essential for cell growth and replication; a deficiency of either one results in defective DNA synthesis and abnormalities in cell

maturation; changes are most evident in tissues with high turnover rates (such as the hematopoietic system).

Vitamin B12 is therefore required for normal hematopoiesis, myelin synthesis, and nervous system integrity. The neuropathology has been attributed to methionine synthetase deficiency. Vitamin B12 acts as a coenzyme for a critical methyl transfer reaction that converts homocysteine to methionine and for a separate reaction that converts L-methylmalonyl-CoA to succinyl-CoA; optic neuropathy has also occurred rarely with vitamin B12 deficiency.

Vitamin B12 deficiency may result in neurological symptoms such as paresthesia, decreased deep tendon reflexes, unsteadiness, confusion, memory loss, gait impairment, polyneuritis (particularly sensory, in the distal extremities), ataxia, and others. Other symptoms may include anemia, optic atrophy, and others.

The causes of vitamin B12 deficiency are varied and include, among others, inadequate intake and inadequate secretion of intrinsic factor.

Hematologic effects of vitamin B12 deficiency include pallor of the skin. Neurologic complications are common in individuals with clinically observable vitamin B12 deficiency and include sensory complaints in the extremities.

Tribemin is an association of B complex vitamins that has been shown to be useful as a reinforcement of the anti- inflammatory treatment of muscle and back pain.

The combination of vitamins B1, B6 and B12 has been shown to have a synergistic effect when combined with NSAIDs in the treatment of pain.

In several randomized studies that have evaluated the effect of the association of the vitamin complex B1, B6 and B12 orally together with diclofenac (NSAID) in more than 1,300 patients with low back pain, it has been shown that the association of this vitamin complex enhances the effect of the NSAID, decreasing the intensity of the pain and accelerating recovery, which allows to reduce the dose and duration of the treatment.

treatment with NSAIDs in these patients.

In these studies, a statistically significant difference in favour of the combination of diclofenac and vitamin B complex was observed in the reduction of pain, as well as a tendency in favour of the combination in the affective area. Also, the number of patients who were able to finish the treatment before the end of the study due to relief of symptoms was significantly higher in patients treated with the combination of NSAID and vitamin B than in patients who took the NSAID alone.

5.2 Pharmacokinetic properties

Vitamins B1, B6 and B12 are well absorbed in the gastrointestinal tract, widely distributed in tissues, excreted mainly in urine and passed into breast milk.

Thiamine

Thiamine in small amounts is well absorbed by an active transport mechanism in the gastrointestinal tract; in high doses thiamine is absorbed by passive diffusion; alcohol inhibits its absorption. Absorption occurs after phosphorylation in epithelial cells and is maximal in the duodenum.

Thiamine is distributed in almost all tissues and is stored mainly in the liver, brain, heart and kidney, where it is converted into diphosphate and triphosphate esters. Thiamine phosphates can be hydrolyzed by phosphatases and thiamine can undergo numerous transformations. Thiamine is not stored in appreciable quantities.

Thiamine is metabolized in the liver in animals.

Its excretion occurs mainly through urine, little or not at all unchanged; quantities in excess of daily requirements are excreted untransformed and as metabolites.

Pyridoxine

Dietary vitamin B6 is absorbed by intestinal mucosal cells through phosphorylation coupled with passive diffusion, mainly in the jejunum and ileum. It is readily absorbed except in malabsorption syndromes.

A large percentage of the body's vitamin B6 is found in the enzyme phosphorylase, which converts glycogen to glucose-1- phosphate. Pyridoxal phosphate (PLP) is present in plasma as an albumin-PLP complex and in erythrocytes it is combined with hemoglobin. Vitamin B6 crosses the placenta and is distributed in breast milk.

Vitamin B6 is excreted renally, almost entirely as metabolites. At very high doses of pyridoxine, a large part of the dose is excreted in the urine without any transformation; it is probably also excreted to a certain extent in the faeces.

Cyanocobalamin

Vitamin B12 requires intrinsic factor, a glycoprotein secreted by the gastric mucosa, for its active absorption in the gastrointestinal tract. Absorption is impaired in patients with a lack of intrinsic factor, malabsorption syndrome, or intestinal abnormalities.

Absorption by passive diffusion also occurs to a small extent.

Vitamin B12 binds extensively to specific plasma proteins called transcobalamins; transcobalamin II appears to be involved in the rapid transport of cobalamins to tissues.

Vitamin B12 is stored primarily in the liver. Vitamin B12 diffuses to the placenta and is distributed in breast milk.

Vitamin B12 is excreted in bile and undergoes extensive enterohepatic circulation. Between 50% and 98% of an intramuscular or subcutaneous dose (between 100 and 1000 micrograms) of cyanocobalamin is excreted unchanged in the urine; most of it during the first 8 hours after injection, but this is thought to be only a small fraction of the reduction in body stores from the diet. Excesses above the daily amount are largely excreted unchanged in the urine. Doses greater than 100 micrograms of vitamin B12 will not result in increased retention of the vitamin, although stores may be replenished more rapidly.

5.3 Preclinical safety data

With vitamin B6, cases of ataxia have been observed in dogs and rats after repeated administration of high daily doses.

Animal studies with vitamin B12 have revealed adverse effects on the fetus (teratogenic or other effects).

Toxicity tests carried out on various animal species have shown that the toxic effects of B vitamins occur at doses much higher than those used.

6. Pharmaceutical particulars

6.1 List of excipients

Povidone, Microcrystalline Cellulose, Magnesium Stearate, Colloidal Silicon Dioxide Eudragit L, Titanium Dioxide, Red Lake No 3, Polyethylene Glycol 6000, Polysorbate 80, Dibuthyl Phthaiate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

Store below 25°C

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6.5 Nature and contents of container

Blister packaging containing pink tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing authorisation holder

Sam-On Ltd.

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Bat-Yam 59602

8. Marketing authorisation number(s)

040-39-22836-00

9. Date of revision of the text

12/2024