SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
TRIBEKSOL 250 mg / 250 mg / 1 mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active substance(s):
Vitamin B_1 (Thiamine mononitrate)_____250 mg
Vitamin B_6 (Pyridoxine hydrochloride)_____250 mg
Vitamin B_{12} (Cyanocobalamin)_____1 mg
Excipient(s) with known effect:
Lactose anhydrous (from cow's milk)_____14 mg
Ponceau 4R_____0.07 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film-coated tablets.
Pink, round, slightly convex, film-coated tablets with a characteristic odor (Vitamin B_1).

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
It is used in patients with combined deficiency or with risk factors for deficiency of vitamins B_1, B_6 and B_{12}.

4.2 Posology and method of administration
Posology / Frequency and duration of administration
If not recommended otherwise by the physician:
For adults: 1 film-coated tablet per day.

The use and safety of TRIBEKSOL in children and adolescents under 18 years of age have not been tested to date.

The product is usually used for one to several weeks. In some cases, the physician may extend the treatment period by several months.

Method of administration
Film-coated tablets should be taken orally and swallowed whole with some liquid.

Additional information on special populations
Renal/Hepatic impairment
Since it contains high doses of B vitamins, it is contraindicated in patients with renal or hepatic impairment (see section 4.3).

Pediatric population
Since it contains high doses of B vitamins, it is contraindicated in children and adolescents under 18 years of age (see section 4.3).

Geriatric population
No specific dose is recommended.

Other
Since it contains high doses of B vitamins, it is contraindicated during pregnancy and lactation (see section 4.3).

4.3 Contraindications

- Hypersensitivity to any ingredient of the medicine
- Pregnancy and lactation
- In children and adolescents under 18 years of age
- Renal or hepatic failure

4.4 Special warning and precautions for use

The recommended dose and treatment duration should not be exceeded.

Due to the high dose of vitamin B_6 content, overdose may lead to serious neurotoxicity (see section 4.9).

Since vitamin B_{12} can stimulate the growth of malignant tumors, TRIBEKSOL should not be given to tumor patients.

Vitamin B_6 accelerates the metabolism of levodopa administered for a treatment, thus reduces its effect. Therefore, vitamin B_6 should not be used at doses much higher than the daily requirement of 2 mg in patients treated with levodopa. This interaction does not occur when the patient is concurrently administered a peripheral decarboxylase inhibitor or a combination of levodopa and decarboxylase inhibitor.

The use of vitamin B_{12} is not recommended in patients with Leber disease as it may increase the risk of optic atrophy.

Hypokalemia, thrombocytosis and sudden death may occur when patients with severe megaloblastic anemia are administered intensive treatment with vitamin B_{12}.

This medicinal product contains lactose anhydrous. This medicinal product should not be used in patients with rare hereditary galactose intolerance, Lapp lactase insufficiency, or glucose-galactose malabsorption.

It may cause allergic reactions due to its excipient ponceau 4R.

4.5 Interaction with other medicinal products and other forms of interaction

Drug interactions:

Vitamin B_1 (thiamine):

- Thiosemicarbazone and 5-fluorouracil inhibit the efficacy of thiamine.
- Antacids inhibit the absorption of thiamine.

Vitamin B_6 (pyridoxine):

Various medications can interact with pyridoxine, causing lower pyridoxine levels. These medications include:

- Cycloserine
- Hydralazines
- Isoniazid
- Desoxypyridoxine
- D-penicillamine
- Oral contraceptives
- Alcohol

Vitamin B_6 (pyridoxine hydrochloride) may decrease the efficacy of the following medicines:
- L-Dopa
- Altretamine
- Phenobarbital
- Phenytoin

Amiodarone: Co-administration of pyridoxine worsens amiodarone-induced photosensitivity.

Vitamin B_{12} (cyanocobalamin):
Excessive alcohol intake for more than 2 weeks, aminosalicylates, colchicine, especially in combination with aminoglycosides, histamine (H2) receptor antagonists, metformin and related biguanides, neomycin, cholestyramine, potassium chloride, methyldopa and cimetidine, oral contraceptives and proton pump inhibitors may reduce the absorption of vitamin B_{12} from the gastrointestinal tract; vitamin B_{12} requirement is increased in patients receiving these treatments.

High and sustained doses of folic acid may decrease blood concentrations of vitamin B_{12}.

Ascorbic acid may deplete vitamin B_{12}. High amounts of vitamin C should be avoided 1 hour after oral intake of vitamin B_{12}.

Patients treated with chloramphenicol may respond poorly to this drug. Chloramphenicol may delay or interrupt the reticulocyte response to vitamin B_{12}. Therefore, blood counts should be closely monitored if this combination cannot be avoided.

Interference with laboratory tests: Vitamin B_1:
- Thiamine may cause false positive results in urobilinogen determination using Ehrlich's reagent.
- High doses of thiamine may interfere with spectrophotometric determination of serum theophylline concentrations.

Vitamin B_6:
Urobilinogen: Pyridoxine may cause a false positive result in a spot test with Ehrlich reagent.

The above information are based on the data from literature.

Additional information on special populations
Pediatric population
No interaction studies have been conducted with TRIBEKSOL.

4.6 Fertility, pregnancy and lactation

General recommendation
Pregnancy category is X.

Women of childbearing potential / Contraception
Women of childbearing potential should use an effective birth control method during treatment.

Pregnancy
It is contraindicated during pregnancy (see section 4.3).

Lactation
It is contraindicated during lactation (see section 4.3).

Reproductive ability / Fertility
To date, no evidence has been shown that this product causes adverse effects on human fertility.

4.7 Effects on ability to drive and use machines
The product has no or negligible effects on the ability to drive and use machines.

4.8 Undesirable effects
Evaluation of undesirable effects is based on the following frequencies: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); Not known (cannot be estimated from available data).

The listed undesirable effects are based on spontaneous reports. Therefore, the above frequency classification is not convenient.

Immune system disorders
Rare : Anaphylaxis and fever.
Not known : Allergic reactions (rash, hives, itching, difficulty breathing, chest tightness, swelling of the face, mouth, and lips or tongue) and shock.

Asthma syndrome, mild to moderate hypersensitivity reactions affecting the skin and/or respiratory tract, gastrointestinal tract and/or cardiovascular system.

Symptoms include rash, urticaria, itching, hives, edema, facial edema, erythema, skin swelling, pruritus, skin redness, allergic edema and angioedema, diarrhea, abdominal pain, respiratory distress, tachycardia, palpitations, shock, feeling of swelling throughout the body, skin numbness or tingling, dyspnea, hypotonia and/or cardio-respiratory distress.

Treatment should be stopped if allergic reactions develop.

Nervous system disorders
Not known : Dizziness, headache, peripheral neuropathy and polyneuropathy, somnolence, paresthesia.

Gastrointestinal disorders
Not known : Diarrhea, dyspepsia, nausea, vomiting, gastrointestinal and abdominal pain.

Skin and subcutaneous tissue disorders
Rare : Allergic reactions including urticarial exanthema, exanthematous rash, skin reactions and angioedema.
Not known : Photosensitivity reactions, rash, erythema, pruritus, bullous dermatitis, acne (high doses of B_{12} may cause acne).

Renal and urinary tract disorders
Not known : Abnormal urine odor.

Laboratory tests
Not known : Increase in aspartate aminotransferase, decrease in blood folate levels.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose and treatment
There is no evidence that this product can cause an overdose if used as recommended.

Neuropathy, which may occur with vitamin B_6 overdose, has been most commonly reported after chronic intake of vitamin B_6 at doses of 200 mg to 6000 mg/day for months or years.

Vitamin B_1 causes almost no adverse effects other than rare allergic reactions, as evidenced by its use as an oral supplement at doses of hundreds of milligrams over many years or even after intravenous injection at repeated doses of 100 mg daily.

Considering that virtually no adverse events have been reported, there is no need to establish a maximum Tolerable Upper Limit (UL) according to the relevant group of nutritionists. Accordingly, the toxic dose of vitamin B_1 is unknown.

The general evidence is that vitamin B_{12} is virtually non-toxic, regardless of the route of administration (oral, parenteral). There are no observed adverse effects when vitamin B_{12} is used at extremely high oral (3000 mcg/day) or parenteral (1000 mcg/day) intake levels. As a result, the maximum Tolerable Upper Limit (UL) for vitamin B_{12} has not been determined by the relevant group of nutritionists and, accordingly, the toxic dose for vitamin B_{12} has not been established.

Symptoms in the event of an overdose include nausea, headache, sensory and/or peripheral neuropathy, paresthesia, somnolence, increase in serum AST level (SGOT) and decrease in serum folic acid concentrations. These effects resolve after discontinuation of drug use.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Vitamin B_1 in combination with vitamin B_6 and/or vitamin B_{12}
ATC code: A11DB

The active substances contained in TRIBEKSOL are of vital importance in cellular energy production, protein and nucleic acid metabolism.

Vitamin B_1:
Thiamine pyrophosphate (TPP), the coenzymatic form of vitamin B_1, is involved in two basic types of metabolic reactions: decarboxylation of α-ketoacids (*e.g. pyruvate, α-ketoglutarate and branched-chain keto acids)* and transketolation (*e.g. between hexose and pentose phosphates*). Thus, the primary physiological role of vitamin B_1 is to act as a co-enzyme in carbohydrate metabolism that requires TPP for several steps in the breakdown of glucose to generate energy.

In addition to its metabolic role as a co-enzyme, vitamin B_1 also involves in neurotransmitter function and nerve conduction.

Vitamin B_1 in high doses and especially in combination with vitamins B_6 and B_{12} suppresses the transmission of neural stimuli and thus can exert an analgesic effect.

Early stages of vitamin B_1 deficiency may be accompanied by nonspecific symptoms that may be overlooked or easily misinterpreted. Clinical signs of deficiency include anorexia, weight loss, mental changes such as apathy, short-term memory loss, confusion and irritability, muscle weakness, cardiovascular effects such as heart enlargement.

Conditions that often accompany marginal vitamin B_1 deficiency and require supplementation are regular alcohol consumption, high carbohydrate intakes and heavy physical exercises.

The functional consequences of severe vitamin B_1 deficiency are cardiac failure, muscle weakness, and peripheral and central neuropathy. Clinical symptoms of beriberi (severe vitamin B_1 deficiency) change with age. Adults may have dry (paralytic or nervous), wet (cardiac), or cerebral (Wernicke-Korsakoff syndrome) forms of beriberi. These disorders should be treated immediately with vitamin B_1. Severe cases of vitamin B_1 deficiency in industrialized countries are likely to be associated with limited food consumption combined with high alcohol consumption. In such cases, renal and cardiovascular complications are life-threatening.

Vitamin B_6:
Vitamin B_6 is pyridoxine hydrochloride. It is converted into pyridoxal phosphate, which is the coenzyme of various metabolic transformations. Pyridoxine is very important for human nutrition.

Vitamin B_6 is a coenzyme for more than 100 enzymes involved in amino acid and protein metabolism, including aminotransferases, decarboxylases, racemases and dehydratases. It is a coenzyme both for δ-aminolevulinate synthase, which catalyzes the first step in its biosynthesis, and for cystathionine ß-synthase and cystathioninase enzymes that play a role in the transsulfuration pathway from homocysteine to cysteine. Most of the total vitamin B_6 in the body is found in the phosphorylase muscle ligament.

The high rate of amino acid production and degradation is an important parameter for the central nervous system to function effectively and efficiently; therefore, a sufficient and appropriate supply of vitamin B_6 is required. It plays an important role in the synthesis of biogenic amines and neurotransmitters in the brain. Vitamin B_6 is required as a coenzyme for the conversion of glutamic acid to GABA (an inhibitory neurotransmitter in the central nervous system). Vitamin B_6 is also required for the conversion of tyrosine to dopamine and noradrenaline, tryptophan to 5-hydroxytryptamine, and histidine to histamine.

Classic clinical symptoms of vitamin B_6 deficiency are:
- Skin and mucosal lesions such as seborrheic dermatitis, glossitis and buccal erosions. Peripheral neuritis with nerve degeneration causing sensory disturbances, polyneuropathies.
- Cerebral convulsions with electroencephalographic abnormalities.
- Hypochromic anemia with microcytosis.
- Impairment of lymphocyte proliferation and maturation, antibody production and T-cell

activities.
- Depression and confusion.
- Impairment in platelet function and coagulation mechanisms.

Many drugs can lead to vitamin B_6 deficiency due to their activities as pyridoxine antagonists. There drugs include:
- Cycloserine, an antibiotic
- Hydralazines
- Isoniazid, a tuberculostatic
- Desoxypyridoxine, an antimetabolite
- D-penicillamine, a copper-binding agent
- Oral contraceptives
- Alcohol

Other factors that cause a decrease in vitamin B_6 are diseases and pathological conditions such as asthma, diabetes, renal disorders, heart disease and breast cancer. A number of conditions are treated with higher doses of vitamin B_6 (premenstrual syndrome, carpal tunnel syndrome, depressions and diabetic neuropathy).

Vitamin B_6 in concentrations of 30 to 100 mg/day is often prescribed as first-line treatment of nausea and vomiting in pregnancy.

Appropriate doses of vitamin B_6 also protect patients against the side effects of radiation therapy.

Vitamin B_{12} (cobalamin):
Vitamin B_{12} is a cofactor for two enzymes: Methionine synthase (an essential reaction for tetrahydrofolic acid regeneration) and L-methylmalonyl-CoA mutase. Methionine synthase requires methylcobalamine as a cofactor for methyl transfer from methyltetrahydrofolate to homocysteine, which ultimately consists of methionine and tetrahydrofolate. L-Methylmalonyl-CoA mutase requires adenosylcobalamin to eventually convert L-methylmalonyl-CoA to succinyl-CoA in an isomerization reaction. In B_{12} deficiency, folate may accumulate in the serum as a result of the B_{12}-dependent methyltransferase slowdown. It is important to provide a suitable and sufficient supply of B_{12} for normal blood formation and neurological function. Vitamin B_{12} is a cofactor for catechol-O-methyl transferase, which plays an important role in the breakdown of catecholamines, namely noradrenaline and dopamine, in the synaptic cleft.

High doses of vitamin B_{12} (combined with vitamins B_1 and B_6) have an analgesic effect.

The major cause of clinically observable B_{12} deficiency is pernicious anemia. The hematological effects of B_{12} are cold skin associated with a gradual onset of common anemia symptoms such as decreased energy and exercise tolerance, fatigue, shortness of breath, and palpitations. The underlying mechanism of anemia is an interference with normal deoxyribonucleic acid (DNA) synthesis. Hematological complications resolve completely with treatment with B_{12} supplements.

75 – 90% of people with clinically observable B_{12} deficiency have neurological complications, and only approximately 25% of cases may be clinical manifestations of B_{12} deficiency. Sensory disturbances (tingling and numbness) in the extremities (more in the lower extremities) are

included in the neurological symptoms. Vibration and position senses are particularly affected. Motor impairments occur, including gait abnormalities. Cognitive changes can occur, with or without mood changes, ranging from loss of concentration to memory loss, disorientation, and distinct dementia. In addition, visual disturbances, insomnia, impotence, and impaired bowel and bladder control may occur. Although the progression of neurological symptoms varies, it usually occurs gradually. Whether neurological complications improve after treatment depends on the duration of these complications.

TRIBEKSOL, which is a combination of vitamins B_1, B_6 and B_{12} in pharmacological doses, shows antalgic, antineuritic, detoxifying and antianemic properties. These vitamins, which are found together in nature, complement each other in terms of their functions on the metabolism of cells, especially the cells of the nervous system. Consequently, TRIBEKSOL shows an effect much more than the effect that can be achieved by using these vitamins individually.

In summary: Vitamin B_1 is essential for proper carbohydrate metabolism and plays an important role in the decarboxylation of alpha keto acids. In addition to its metabolic role as a coenzyme, vitamin B_1 also involves in neurotransmitter function and nerve conduction. The nervous system and heart are particularly sensitive to the effects of vitamin B_1 deficiency. As a result, the most severe forms of thiamine deficiency, Wernicke Encephalopathy, Korsakoff Psychosis, and Beriberi, predominantly affect these systems.

Vitamin B_6 (pyridoxine and related compounds) functions as a coenzyme in the metabolism of amino acids, glycogen and lipids, and in the synthesis of nucleic acids.

Classic symptoms of vitamin B_6 deficiency are skin and mucosal lesions (e.g. seborrheic dermatitis), microcytic anemia, cerebral convulsions, depression and confusion.

Vitamin B_{12} acts as a coenzyme for an important methyl transfer that converts homocysteine to methionine and for a separate reaction that converts L-methylmalonyl-CoA to succinyl-CoA. Adequate B_{12} supplementation is essential for normal blood formation and neurological function.

The major cause of clinically observable B_{12} deficiency is pernicious anemia. Hematological effects of B_{12} deficiency include skin pallor associated with the gradual onset of the common anemia symptoms. Neurological complications are common in individuals with clinically observable B_{12} deficiency and include sensory impairments in the extremities.

5.2 Pharmacokinetic properties

General properties

Vitamin B_1 (thiamine):

Absorption:

Thiamine is well absorbed from the gastrointestinal tract following oral administration, but absorption is limited at high doses. Its absorption is mediated by two different mechanisms: through carrier-based transport at low physiological concentrations (<2 mcm), and through passive diffusion at higher concentrations. Its absorption is generally high, but intestinal absorption in humans is rate-limited.

The need for vitamin B_1 is directly related to the intake of carbohydrates: 0.5 mg per 1,000

calories. High-calorie and especially high-carbohydrate food intake proportionally increases thiamine requirement.

Distribution:
Vitamin B_1 is widely distributed into body tissue and found in breast milk. Inside the cell, thiamine mostly occurs as diphosphate. The average total amount of vitamin B_1 in adult humans is about 30 mg. It is most commonly found in the heart (0.28-0.79 mg per 100 g), followed by kidney (0.24-0.58), liver (0.2-0.76), and brain (0.14-0.44). The level of vitamin B_1 in the spinal cord and brain is approximately twice that in the peripheral nerves. Whole blood vitamin B_1 ranges from 5 to 12 mcg/100 mL; 90% of it is found in red blood cells and leukocytes. The concentration found in leukocytes is 10 times higher than that in red blood cells. The rate of production and breakdown of vitamin B_1 in the body is relatively higher and is never stored in large amounts in tissues. Therefore, it must be supplied continuously. Insufficient intake can cause signs of biochemical and subsequent clinical deficiency. When vitamin B_1 intake is about 60 mcg per 100 g of body weight (or 42 mg per 70 kg) and when total body vitamin B_1 is 2 mcg/g (or 140 mg per 70 kg), a plateau level is reached in most tissues.

There are two other mechanisms involved in the transfer of vitamin B_1 within the blood-brain barrier. However, the saturable mechanism in the blood-brain barrier is different from the energy-dependent mechanism in the intestine and the active transport system in cerebral cortex cells, which is based on membrane-bound phosphatases. The immunohistochemical distribution of thiamine pyrophosphate (TPP) shows that it plays a role in nerve conduction.

Biotransformation:
Oral (or parenteral) thiamine rapidly converts in tissues to dysphosphate and, to a lesser extent, triphosphate esters. All vitamin B_1 in excess of tissue needs, binding and storage capacity is rapidly excreted in the urine. In rats, the parenteral intake of thiamine of 10 mcg/100 mg body weight (or 7 mg per 70 kg) has been proven to be sufficient for proliferation but less than normal tissue levels. Stimulation of the nerves causes the release of thiamine or monophosphate with a simultaneous decrease in tri- and diphosphatases.

Elimination:
Thiamine is not stored in significant amounts in the body and more than the body needs is excreted in the urine as unchanged thiamine or metabolites. In humans, when oral doses higher than 2.5 mg are administered, there is a small increase in urinary vitamin B_1 excretion. The half-life of vitamin B_1 in the body is 10-20 days. In addition to free vitamin B_1 and small amounts of thiamine diphosphate, thiochrome, and thiamine disulfide, approximately 20 or more vitamin B1 metabolites have been reported in the urine of rats and humans, but only six of them were actually determined and identified. The ratio of metabolites compared to excreted vitamin B_1 increases with decreasing vitamin B_1 intake.

Vitamin B_6 (pyridoxine):
Absorption:
Pyridoxine hydrochloride is absorbed from the gastrointestinal tract and converted to the active forms pyridoxal phosphate and pyridoxamine phosphate. Various dietary forms of vitamin B_6 are absorbed by intestinal mucosal cells through passive diffusion-dependent phosphorylation, especially in the jejunum and ileum (intestine).

Distribution:

Pyridoxine hydrochloride crosses the placental barrier and found in breast milk. B_6 forms are converted into pyridoxal phosphate (PLP) and pyridoxamine phosphate (PMP) in the liver, erythrocytes and other tissues. These compounds are distributed in animal tissues, but none are stored. The majority of the body's vitamin B_6 is found in phosphorylase, the enzyme that converts glycogen into glucose 1-phosphate. About half of the vitamin B_6 in the body can reflect the phosphorylase of skeletal muscle. PLP can be found in plasma as a PLP-albumin complex and in erythrocytes in conjunction with hemoglobin. The concentration of PL in the erythrocyte is 4 to 5 times the concentration in plasma.

Biotransformation:
PLP and PMP, in particular, act as coenzymes in transamination reactions. In particular, PLP acts as a cofactor for many enzymes involved in the synthesis or catabolism of amino acids. PLP is also involved in the decarboxylation and racemization of A-amino acids, other metabolic transformations of amino acids, and the metabolism of lipids and nucleic acids. It is also the basic coenzyme for glycogen phosphorylase. Pyridoxal phosphate is also required for the synthesis of δ-aminolevulinic acid, which is a precursor of heme.

Elimination:
Normally, the major excretion product is 4-pyridoxic acid; this corresponds to about half of the B_6 compounds in urine. With higher doses of vitamin B_6, the proportion of other forms of vitamin B_6 also increases. At very high pyridoxine doses, most of the dose is excreted unchanged in the urine. B_6 is probably also excreted in the faeces in limited quantities, but is difficult to quantify due to microbial synthesis of B_6 in the gut.

Vitamin B_{12} (cobalamin):
Absorption:
The intestinal absorption of cobalamins depends on the glycoprotein intrinsic factor. As mentioned above, the terms vitamin B_{12} and cobalamin refer to all members of a group of high cobalt-containing compounds (corrinoids). Corrinoids can be converted to two cobalamin coenzymes active in human metabolism. Cyanocobalamin is the commercially available form of vitamin B_{12}.

Cobalamins can be absorbed by two different mechanisms: an active mechanism (protein-based) and a diffusion-type mechanism. A small amount of vitamin B_{12} is absorbed through the active process that requires an intact stomach, intrinsic factor (a glycoprotein secreted by the parietal cells of the stomach after stimulation with food), pancreatic competence and terminal ileum with normal functioning. In the stomach, food-bound B_{12} is broken down from proteins due to acid and pepsin. The released B_{12} then binds to R proteins (haptocorrins) secreted through the salivary glands and gastric mucosa. In the small intestine, pancreatic proteases partially degrade R proteins and released B_{12} binds to the intrinsic factor. The resulting intrinsic factor and B_{12} complex bind to specific receptors in the ileal mucosa; after internalization of the complex, B_{12} enters the enterocyte. After about 3 to 4 hours, B_{12} is recirculated. At dose levels up to 10 mcg, the efficiency of this mechanism is approximately 50%. At dose levels higher than 10 mcg, the efficiency and effectiveness of absorption decrease. The second absorption mechanism occurs by diffusion at a very low rate and shows an efficiency and efficacy corresponding to about 1% and only provides a quantitatively statistically significant result at oral doses exceeding 100 mcg.

B_{12} malabsorption occurs if there is a deficiency in the intrinsic factor (the condition in

pernicious anemia). If this condition is not treated, potentially irreversible neurological damage and life-threatening anemia occurs.

Distribution:
Cobalamins are rapidly transported into the blood to bind to protein known as transcobalamins. Cobalamins are stored in the liver and excreted in bile. They are known to cross the placenta. The predominant forms in plasma and tissue are methylcobalamin, adenosylcobalamin and hydroxocobalamin. Methylcobalamin accounts for 60% to 80% of the total plasma cobalamin. In normal humans, cobalamins are found mainly in the liver, where the average amount is 1.5 mg. Kidneys, heart, spleen and brain each contain about 20-30 mcg. Mean values for the total body content calculated for adult humans are 2-5 mg. The pituitary gland is the tissue with the highest concentration per gram of organs/tissues. Adenosylcobalamin is the major cobalamin among all cellular tissues, accounting for about 60-70% in the liver and about 50% in other organs.

Biotransformation:
As vitamin B_{12} passes through the intestinal mucosa, it is transferred to the plasma transporter protein transcobalamin II, which delivers the vitamin to the cells. The specific biochemical reactions in which cobamide coenzymes play a role are of two types: (1) reaction involving 5-deoxyadenosine covalently attached to the cobalt atom (adenosylcobalamin) and (2) reaction with a methyl group attached to the central cobalt atom (methylcobalamine). Coenzyme methylcobalamin catalyzes a transmethylation from a folic acid cofactor to homocysteine and forms methionine. This reaction releases the unmethylated folate cofactor for other single-carbon transfer reactions which are important for nucleic acid synthesis. The other cobalamin coenzyme, deoxyadenosylcobalamin, catalyzes the conversion of methylmalonyl-coenzyme A to succinyl-coenzyme A, a reaction in the degradation pathway of certain amino acids and single-chain fatty acids.

Vitamin B_{12} deficiency causes macrocytic, megaloblastic anemia, neurological symptoms due to demyelination of the spinal cord, brain, optic and peripheral nerves, and other less specific symptoms (e.g. tongue pain, weakness). In the absence of anemia, and especially in the elderly, neuropsychiatric symptoms of vitamin B_{12} deficiency are observed.

Elimination:
Urinary, biliary and fecal pathways are the main pathways of excretion. Only unbound plasma cobalamin is available for urinary excretion, and thus urinary excretion through glomerular filtration of free cobalamin is minimal: i.e. varying at levels up to 0.25 mcg per day. About 0.5-5 mcg of cobalamin per day is secreted into the digestive system, mainly bile; at least 65-75% is reabsorbed in the ileum via the intrinsic factor mechanism. The reversal of this effective B12 enterohepatic circulation, which occurs in the bile and other intestinal secretion channels, does not function in the presence of pernicious anemia due to insufficient intrinsic factor activity. Total loss in the body ranges from 2 to 5 mcg per day. Thus, daily loss of vitamin B_{12} corresponds to approximately 0.1% of the body pool (in the range of 0.05-0.2%), regardless of the total size.

In summary: Vitamin B_1 is well absorbed from the gastrointestinal tract by a carrier-based transport and, at higher concentrations, by passive diffusion. Vitamin B_1 is widely distributed in body tissues. The plasma half-life of vitamin B_1 is 24 hours and it is not substantially stored in the body. Excess thiamine taken into the stomach is excreted in the urine as free vitamins or

metabolites.

Vitamin B_6 is well absorbed in the gastrointestinal tract. Vitamin B_6 is widely distributed in all body tissues. Once vitamin B_6 is absorbed, it is converted into pyridoxal 5-phosphate, which is the active coenzyme form. Muscle is the primary site of storage for pyridoxal 5-phosphate. The major excretion product of vitamin B_6 is 4-pyridoxic acid, which accounts for approximately half of the vitamin B_6 compounds in urine.

Vitamin B_{12} is absorbed by an active (protein-based) and a diffusion-type mechanism. Small amounts of vitamin B_{12} are absorbed by active processes that require a healthy stomach, intrinsic factor, pancreatic competence, and a normal functioning terminal ileum. Vitamin B_{12} is widely distributed in body tissues. Excretion is mainly by urinary, biliary and fecal routes.

5.3 Preclinical safety data
Although no specific studies have been conducted with this product, the preclinical safety of its individual components has been extensively documented.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Povidone K 90 (Plasdone K 90)
Microcrystalline cellulose (Avicel PH 112 SLM)
Croscarmellose sodium (Ac-di-sol)
Lactose anhydrous (from cow's milk)
Magnesium stearate

Film coating materials:
Opadry 0Y-24931 pink
- Titanium dioxide
- Polyethylene glycol 400
- Ponceau 4R
- Indigo carmine
- Quinoline yellow

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
48 months.

6.4 Special precautions for storage
Store at room temperature below 25°C. Keep away from humidity.

6.5 Nature and contents of container
Film-coated tablets of 30 or 50 in PVC/PVDC Al blister packs.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local

requirements.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No: 1
34303 Küçükçekmece / İSTANBUL / TÜRKİYE

8. MARKETING AUTHORIZATION NUMBER(S)

139 / 67

9. DATE OF FIRST AUTHORIZATION/ RENEWAL OF THE AUTHORIZATION

Date of first authorization : 29.07.1986
Date of last renewal :

10. DATE OF REVISION OF THE TEXT

29.01.2024