PROSPECTUS

BEHEPTAL AMPOULE, 2 ml

STERILE-APYROGEN

FORMULA: In each ampoule;

Thiamine hydrochloride ..... 25.0 mg
Pyridoxine hydrochloride……10.0 mg
Riboflavin 5-phosphate .....5 mg
Cyanocobalamin .....0.03 mg
D-Panthenol……..5.0 mg
Niacinamide ..... 50.0 mg
Benzyl alcohol .....24.0 mg
Diethanolamine …… 4.0 mg
Water for injection q.s. .....2 ml

PHARMACOLOGICAL PROPERTIES:

Group B vitamins are in cell and tissues, enzyme systems that regulate carbohydrate, fat and protein metabolisms which are very important for life and development. As they are widely found together in nature, they need to enter to organism together in order to provide an optimal effect.

Thiamine hydrochloride provides normal growth of cells, regulates appetite, digestion and absorption. It acts as a co-enzyme in carbohydrate metabolism.

Pyridoxine hydrochloride is effective in the use of unsaturated fatty acids and protein metabolism.

It acts as a co-enzyme in amino acid metabolism. Riboflavin constitutes the most important part of the oxidase enzyme required for the desamination of amino acids in protein metabolism. Its active form is riboflavin phosphate and flavin adenine dinucleotide.

Cyanocobalamin; It is found in very small amounts in foods containing animal protein and is an important nutritional factor. It is necessary for nucleic acid metabolism and normal blood production. Another important effect is to maintain the normal structure and function of some neurons in the central and peripheral nervous system.

D-panthenol; It is found in the structure of the co-enzyme A, which has an important role

in the development of the organism.

Niacinamide; It is an important vitamin in nutrition since it enters the structure of coenzymes involved in the oxidation-reduction events of the cells. Co-enzyme I and co-enzyme II are useful in converting carbohydrates into protein.

B Group vitamins are easily absorbed from the gastrointestinal tract and the injection site and excreted in the urine.

INDICATIONS:

It is used as vitamin B complex in disorders related to deficiency of B group vitamins.

Vestibule of mouth disorders: Stomatitis,

Gastro-intestinal disorders: Colitis, ulcerative colitis, chronic enteritis, sprue, absorption disorders, atonic constipation, diarrhea,

Liver disorders: Epidemic hepatitis, treatment of fatty degeneration of liver and prophylaxis of liver diseases.

Skin disorders: Chronic eczema, neurodermatitis, radiation dermatoses, toxic and drug-induced dermatosis and eczema, acne, furunculosis, pruritus, nail and hair breakage, skin dryness, pallegra,

Nervous system disorders: Neuritis and neuralgia, shingles, sciatica, infectious drug-related nervous disorders, Korsakoff's disease,

Generally: It is indicated in cases of weakness, loss of appetite, weight loss, infection and convalescence in growing children, diabetic and ulcerous patients on diet, chronic alcoholism and vomiting of pregnancy.

CONTRAINDICATIONS:

Contraindicated in patients who are sensitive to ingredients.

WARNINGS/PRECAUTIONS:

Due to vitamin B_2 (Riboflavin) which is in composition, it may stain urine to yellow. This situation should not be feared.

Thiamine hydrochloride can cause allergic or anaphylactic reactions. Therefore, when using for patients who have any sensitivity in the past, caution should be exercised.

Intravenous administration as infusion should be performed in hospital and by protecting from light.

SIDE EFFECTS/ADVERSE EFFECTS:

Although almost non-existent and very rare allergic symptoms can be seen in long-term high-dose treatments, it is improved when immediately discontinued.

CONSULT YOUR PHYSICIAN IF AN UNEXPECTED EFFECT IS OBSERVED.

DRUG INTERACTIONS AND OTHER INTERACTIONS:

It reduces the antibacterial activities of Riboflavin, streptomycin, erythromycin, thyrotricin, carbamycin and tetracycline solutions. Intestinal absorption of riboflavin is delayed by probenecid. Since pyridoxine hydrochloride increases the peripheral metabolism of levodopa, it should not be used in patients with Parkinson's disease who are taking levodopa alone. Aminoglycoside antibiotics and long-term cholestramine, chloramphenicol, colchicine, anticonvulsants, potassium preparations, amino salicylic acid, metformin therapy and long-term alcohol use may reduce the absorption of cyanocobalamin from the intestine.

DOSAGE AND METHOD OF ADMINISTRATION:

Based on the case and advice of the physician, 1 or 2 ampoules per day are administered intramuscularly or intravenously in the hospital and protected from light.

STORAGE CONDITIONS:

Store at room temperature between 15-30 ºC, protected from light.

COMMERCIAL PRESENTATION AND PACKING CONTENT:

2 ml x 5 ampoules

2 ml x 100 ampoules

Other Pharmaceutical Dosage Forms Available on the Market:

Beheptal Draje

Sold with prescription.

Do not use without consulting a physician.

Keep out of reach of children and in its package.

Marketing Authorization Date and No: 05.05.1999/191-37

Marketing Authorization Holder and Manucturing Site: OSEL İLAÇ SAN. ve TİC. A.Ş.

Beykoz / İST.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

BEHEPTAL, 2 ml AMPOULE

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Drug substance:

In each 2 ml ampoule;

Thiamine hydrochloride .....25 mg + 25% excess dose = 31.25 mg

Riboflavin 5-phosphate .....5 mg + 10% excess dose = 5.5 mg

Pyridoxine hydrochloride .....10 mg + 10% excess dose = 11.0 mg

Cyanocobalamin .....0.03 mg + 20% excess dose = 0.036 mg

D-panthenol .....5 mg

Niacinamide……..50 mg + 5% excess dose = 52.5 mg

Benzyl alcohol .....24 mg

Diethanolamine.....4 mg

Water for injection……..q.s.....2 ml

3. PHARMACEUTICAL FORM

Small volume parenteral solution

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

It is indicated as vitamin B complex in disorders related to B group vitamins deficiency.

Vestibule of mouth disorders: Stomatitis,

Gastro-intestinal disorders: Colitis, ulcerative colitis, chronic enteritis, sprue, absorption disorders, atonic constipation, diarrhea,

Liver disorders: Epidemic hepatitis, treatment of fatty degeneration of liver and prophylaxis of liver diseases.

Skin disorders: Chronic eczema, neurodermatitis, radiation dermatoses, toxic and drug-induced dermatosis and eczema, acne, furunculosis, pruritus, nail and hair breakage, skin dryness, pallegra,

Nervous system disorders: Neuritis and neuralgia, shingles, sciatica, infectious drug-related nervous disorders, Korsakoff's disease,

Generally: It is indicated in cases of weakness, loss of appetite, weight loss, infection and convalescence in growing children, diabetic and ulcerous patients on diet, chronic alcoholism and vomiting of pregnancy.

4.2. Posology and method of administration

Based on the case and advice of the physician, 1 or 2 ampoules per day are administered intramuscularly or intravenously in the hospital and protected from light.

4.3. Contraindications

Contraindicated in patients who are sensitive to ingredients.

4.4. Special warnings and special precautions for use

Due to vitamin B_2 (Riboflavin) which is in composition, it may stain urine to yellow. This situation should not be feared.

Thiamine hydrochloride can cause allergic or anaphylactic reactions. Therefore, when using for patients who have any sensitivity in the past, caution should be exercised.

Intravenous administration as infusion should be performed in hospital and by protecting from light.

4.5. Interaction with other medicinal products and other forms of interaction

Vitamin B_1 is incompatible with mercury chloride, iodine, carbonate, acetate and iron sulfate, which are oxidizing and reducing substances. Tannic acid forms brown precipitates with ferric ammonium citrate and iodine.

Preparations containing vitamin B_1 are incompatible with phenobarbital sodium and benzyl penicillin.

Solutions containing vitamin B complex are incompatible with solutions containing metabisulfite or dextrose.

Vitamin B_2 is incompatible with alkalines and heavy metal salts. It reduces the antibacterial activities of streptomycin, erythromycin, thyrotricin, carbamycin and tetracycline solutions. Intestinal absorption of vitamin B_2 is delayed by probenecid.

It is incompatible with vitamin B_6, alkaline solutions, iron salts and oxidant solutions. Isoniazid increases the excretion of vitamin B6 from the kidneys. Cycloserine and hydralazine are vitamin B_6 antagonists. Since it increases the peripheral metabolism of levodopa, it should not be given to patients with Parkinson's disease who use only levodopa.

Vitamin B_{12} is incompatible with 10 mg of warfarin sodium in 100 ml dextrose solution, with oxidizing and reducing agents and heavy metal salts. Use of aminoglycoside antibiotics and long-term cholestramine, chloramphenicol, colchicine, anticonvulsants potassium preparations, amino salicylic acid, metformin therapy and long-term alcohol may reduce absorption of vitamin B_{12} from the intestine.

Niacinamide is incompatible with alkalines and mineral acids.

4.6. Pregnancy and lactation

Pyridoxine inhibits lactation and should not be used in lactating women. Vitamin B_{12} deficiency has been reported in children of pernicious anemia or vegetarian mothers. Vitamin B_{12} passes to placenta.

4.7. Effects on ability to drive and use machines

None.

4.8. Undesirable effects

Although almost non-existent and very rare allergic symptoms can be seen in long-term high-dose treatments, it is improved when immediately discontinued.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

B Group vitamins are in cell and tissues, in the ferment systems which are very important for life and development of carbohydrate, fat and protein metabolism. As they are widely found together in nature, they need to enter to organism together in order to provide an optimal effect. Their metabolic events are closely related.

The deficiency or excessive consumption of one of B group vitamins often reduces the function of others and increases the need for them. Therefore, in the case of diseases related to the deficiency of one of B group vitamins, it is generally necessary to give other vitamins in this group together.

Group B vitamins have antitoxic, antinevritic, lipotrophic, antiasthenic and anabolic effects in addition to metabolic effects. Biologically vitamin B_1, vitamin B_2, niacinamide, pantothenic acid and vitamin B_6 show a pharmacological activity that allows the organism to adapt to various pathological conditions. In the diseases of the liver parenchyma, group B vitamins are important besides lipotropic substances. Animal experiments and various clinical studies show that group B vitamins have a protective effect on liver and accelerate the repair of liver parenchyma.

Vitamin B_1

Provides normal growth of cells, regulates appetite, digestion and absorption. It takes place as a co-enzyme in carbohydrate metabolism. Prevents malfunctions in the nervous system. In deficiency, the use of protein and glucose is impaired, fat metabolism is accelerated, in advanced cases beriberi disease may occur.

Vitamin B_2

It binds to a protein colloid in the organism and forms the yellow enzyme of Warburg. This enzyme is involved in oxidoreduction events of carbohydrate metabolism. It is the most

important part of the oxidase enzyme required for the desamination of amino acids in protein metabolism. In case of deficiency, lip sides are chapped, red color in tongue, seborrheic dermatosis in nose and lip fold, vascular formation in cornea and dulling are seen.

Vitamin B_6:

It is a pyridine derivative which is effective in the use of unsaturated fatty acids and protein metabolism. It acts as a co-enzyme in amino acid metabolism. In some pellagra patients, symptoms such as insomnia, irritability, weakness, and difficulty in walking are improved with vitamin B_6 treatment despite nicotinic acid treatment. Tryptophan metabolism is impaired, hypochrome anemia, irritability and convulsions are observed in children who are fed with food free of B_6 vitamin.

Niacinamide:

It is an important vitamin in nutrition since it enters the structure of coenzymes involved in the oxidation-reduction events of the cells. Co-enzyme I and co-enzyme II are useful in converting carbohydrates into protein. It is important in assimilation of plant proteins in foods. In deficiency of it, pellagra disease, mucosal aphthae, pain, atrophy of the tongue, increase in salivary secretion, nausea and diarrhea occur.

D-Panthenol:

It is found in the structure of the co-enzyme A which have an important role in the development of the organism. In deficiency of it, growth deficiency, dermatitis, organic and functional disorders of the nervous system, gastrointestinal disorders and depigmentation of the hair are observed.

Vitamin B_{12}:

It is found as in very small amounts in foods containing animal protein and is an important nutritional factor.

It provides normal erythropoiesis by regulating nucleic acid metabolism in the bone marrow. It is used in the treatment of megaloblastic anemia, painful syndromes associated with neurological disorders and developmental delays due to animal protein deficiency.

5.2 Pharmacokinetic properties

Vitamin B_1

After intramuscular administration, it is rapidly and completely absorbed and disperses in body fluids. It is metabolized in liver of animals. In humans, it is excreted in urine with little or no change after administration of physiological doses.

Vitamin B_6:

It accumulates mainly in liver, in very small amounts in muscles. The amount of vitamin B_6 in the body is 16-27 mg. Its main forms in the blood are pyridoxal and pyridoxal phosphate. It crosses the pyridoxal placenta and plasma concentrations in the fetus are 5 times higher than the mother's plasma concentration. Pyridoxine in erythrocytes is phosphatized to pyridoxine phosphate. Riboflavin is required to convert pyridoxine phosphate to pyridoxal phosphate. Half-life of pyridoxine is 15-20 days. The pyridoxal in the liver is oxidized to 4 - pyridoxic acid and excreted in the urine.

Cyanocobalamin:

Serum cobalamin concentrations increase after intramuscular administration. Hydroxocobalamin is slowly absorbed from the site of injection. Elevation in the liver is more than cyanocobalamin. Cyanocobalamin is dispersed in the liver, bone marrow and other body tissues and passes into the placenta. Vit. B_{12} blood concentration is 3-5 times greater than that of the mother.

It passes into the breast milk of nursing mothers. As i.v. or i.m. 50-90% is excreted in the urine by glomerular filtration within 48 hours.

Vitamin B_2:

The biological half-life of riboflavin after intramuscular administration is 66-84 hours. Its metabolic status is not fully known. In the gastrointestinal mucosal cells, erythrocytes, and the liver phosphoralizes the flavin mononucleotide, which in turn converts to flavin adenindinucleotide in the liver.

Riboflavin can be excreted from kidneys by hemodialysis.

Niacinamide:

It is easily absorbed from the injection site after subcutaneous or intramuscular administration. It is usually dispersed in body tissues. It passes into milk.

It is necessary for physiological functions as a co-enzyme.

Niacinamide is metabolized in the liver to N-methylniacinamide and other N-methyl derivatives. These metabolites are excreted in the urine.

After administration of niacin or niacinamide in physiological doses, a very small amount of niacinamide is excreted in the urine unchanged.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

In each 2 ml ampoule;

Benzyl alcohol ..... 24 mg

Diethanolamine ..... 4 mg

Water for injection q.s. ..... 2 ml

6.2 Definition of Basic Processes in Production:

A quantity of water for injection is cooled to 40ºC from the WFI line with the help of heat exchanger. Thereupon, the fully weighed according batch size Vit. B_1, Vit. B_6, niacinamide and Vit. B_2 is dissolved.

In another container Vit. B_{12} is dissolved in water and added to the process tank. The diethanolamine dissolved in benzyl alcohol and water is then added to the tank and the process tank is completed with water for injection to the batch size volume. It is mixed until homogenous and pH is controlled.

Samples are taken from the top and bottom of the process tank and sent to the quality control laboratory for intermediate analysis. Following the approval of compliance of intermediate analysis, under aseptic conditions, it is filtered through a PALL filter group into a pre-sterilized solution collection tank using a 0.2 micron pore-wide filter. Filtered solution is filled and sealed in 2.0 ml amber colored Type I glass ampoules, pre-washed and sterilized in ampoule washing, sterilization, filling and sealing line under a stream of nitrogen at 2.15 ml per ampoule.

Filled and sealed ampoules are automatically performed for crack tests and optical controls and taken to the quarantine section.

Quality Control Laboratory takes samples for final analyzes and analyze them. Ampoules are packed after compliance report given by Quality Control Laboratory.

6.3 Finished Product Specifications:

Appearance **:** Yellow colored-clear - particle-free solution

pH **:** 4.3 - 4.8

Sterility **:** Sterile

Bacterial Endotoxin Test **:** Complies

Assay:

Tiamine HCl : 25 mg + 25% excess dose = 31.25 mg/2 ml
(Lim. 90.0% - 110.0%)

Pyridoxine HCl	: 10 mg + 10% excess dose = 11.0 mg/2 ml (Lim. 95.0% - 120.0%)
Riboflavin 5-phosphate	: 5 mg + 10% excess dose = 5.5 mg/2 ml (Lim. 95.0% - 120.0%)
Cyanocobalamin	: 0.03 mg + 20% excess dose = 0.036 mg/2 ml (Lim. 95.0% - 115.0%)
Niacinamide	: 50 mg + 5% excess dose = 52.5 mg/2 ml (Lim. 95.0% - 110.0%)

Filling Volume: 2.15 ml (2.1 ml - 2.2 ml)

6.4. Incompatibilities:

Beheptal Ampoule should not be mixed with solutions containing metabisulfite or dextrose, chlorpromazine HCl, ascorbic acid, tetracycline, erythromycin, streptomycin, acidic and alkaline solutions.

6.5. Shelf life:

Shelf life of Beheptal Ampoule is 3 (three) years.

6.6. Special Storage Conditions:

Store at room temperature between 15-30ºC, protected from light.

6.7. Type and Structure of Packaging:

2 ml amber colored Type I glass ampoule

6.8. Patient Information Leaflet *(Prospectus)*:

It is administered intramuscularly, intravenously or as infusion in hospital by protecting from light. Do not use without consulting a physician. Read patient information leaflet *(prospectus)* before use.

7. Prescription/Non-Prescription Sales:

Sold with prescription.

8. Name, Address, Tel and Fax No. of the Marketing Authorisation Holder:

OSEL İLAÇ SAN. ve TİC. A.Ş.
Akbaba Köyü, Fener Cad. No: 115
Beykoz/İST.
Tel: 0 (216) 320 45 50 (Pbx)
Fax: 0 (216) 320 41 45

9. Marketing Authorisation Date And No:

05.05.1999/191-37

10. Name, Address, Tel and Fax No. of Manufacturer:

OSEL İLAÇ SAN. ve TİC. A.Ş.
Akbaba Köyü, Fener Cad. No: 115
Beykoz/İST.

Tel: 0 (216) 320 45 50 (Pbx)

Fax: 0 (216) 320 41 45