SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Neuro-B F. C Tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:
Vitamin B1 (Thiamine Mononitrate) 100 mg.
Vitamin B6 (Pyridoxine Hydrochloride) 100 mg.
Vitamin B12 (Cyanocobalamin) 0.15 mg.

3. PHARMACEUTICAL FORM

White to Pinkish–White, capsules shaped film coated tablets having embossing of UC on one side and plain surface on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adjuvant therapy in neuritis and neuralgia (mono- and polyneuropathies), root irritation due to degenerative changes of the vertebral collumn, lumbago, sciatica, cervical syndrome, shoulder-arm syndrome, for the follow-up treatment of trigeminal neuralgia and for the supportive treatment in facial paresis, herpes zoster.

4.2 Posology and method of administration

For oral use between injections, as a follow up to a course of injections and as prophylactic therapy.
Adults and adolescents over 15 years: 1-2 tablets 1-3 times a day.
Children over 7 years: 1 tablet once a day.
Children under 7 years: on physician's prescription.
To be taken with a little liquid during or after meals.
Duration: The duration of treatment is stated by the physician.

4.3 Contraindications

Neuro-B coated tablets shall not be used in cases under suspicion of hypersensitivity to thiamine or any of the substances.

4.4 Special warnings and precautions for use

Not Applicable.

4.5 Interaction with other medicinal products and other forms of interaction

Patients treated with L-Dopa should not take high doses of pyridoxine (vitamin B6) and thus not Neuro-B, as pyridoxine reduces the effects of L-Dopa.

4.6 Pregnancy and lactation

Under the recommended dosage regime the application of vitamin B1, B6 and B12 during pregnancy has not lead to any untoward effects.
An unphysiological enrichment of the vitamins B1, B6 and B12 in breast-milk during location is not documented.

4.7 Effects on ability to drive and use machines

Not Applicable

4.8 Undesirable effects

In individual cases sweating, tachycardia, and skin reactions accomplished with itching and urticaria have been described.

4.9 Overdose

The vitamin B1, B6 and B12 show a wide therapeutic range. During recommended usage symptoms of overdose are not known to date.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: A11DB

Thiamine

Thiamine and its water-soluble salts are phosphorylated in the body to biologically active thiamine pyrophosphate (TPP) and thiamine triphosphate (TTP). Thiamine has a very specific constitution, i.e. even minor alterations at the molecule produce a reduction in effect, ineffectiveness and in certain cases substances with an anti vitamin character (B1 antagonists). TPP intervenes as a coenzyme in important functions in carbohydrate metabolism. TPP is the coenzyme of pyruvate decarboxylase, 2-oxoglutamate dehydrogenase and transketolase. On account of the close inter-connections of the metabolism interactions take place with the other vitamins in the B complex. Indications of an analgetic effect have been seen in experimental investigation.

Pyridoxine

In its phosphorylated form (pyridoxal-5-phosphate, PALP) pyridoxine, an essential active principle, is the coenzyme of a large number of enzymes which intervene in the entire nonoxidative metabolism of the amino acids. Through decarboxylation they are involved in the formation of physiologically active amines (e.g. adrenalin, histamine, serotonin, dopmaine, tyramine) and through trasamination in anabolic and catabolic metabolic processes (e.g. gluamic-oxaloacetic transaminase, glutamic-pyruvic transaminase, gamma-amino butyric acid, alpha-ketoglutaric transaminase) as well as in various amino acid breaking down and synthesis processes. Vitamin B6 intervenes at 4 different points in tryptophan metabolism.

Within the process of the synthesis of the red blood pigment B6 catalyses the formation of alpha-amino-beta-ketoadipic acid. Furthermore, there are direct biochemical links with other vitamins in the B group. An analgesic effect has been demonstrated in animal experiments.

Cobalamin

Vitamin B12 is an essential active principle for humans. The cyanocobalamin taken up as a pro-drug must first of all be converted to the coenzyme forms methylcobalamin and 5-desoxyadenosyl cobalamin which are effective in humans. Methylcobalamin is required for the formation of methionine from homocysteine. In the methylation of homocysteine to methionine free tetrahydrofolic acid is formed from 5-methyltetrahydrofolic acid. It is

important for erythropoiesis. 5-desoxyadenosyl cobalamin is required for the conversion of methylmalonyl coenzyme A into succinyl coenzyme A. Its absence causes increased propionic acid and methylmalonyl acid levels, which are causes of the formation of abnormal fatty acid chains. On account of the close interconnections of the metabolism inteactions take place with the remaining vitamins in the B complex. Animal studies indicate an antinociceptive effect from vitamin B12.

C ombination of vitamins B1, B6 and B12

Vitamins B1, B6 and B12 are of special importance for the metabolism in the peripheral and central nervous systems because of the part they each play individually and also because of the biochemical links between them, this justifying their combined use.
The effect of thiamine, pyridoxine and cobalamin on the regeneration of nerves has been examined in various animal investigations using the vitamins individually and in combination.

After experimentally induced nerve lesion administration of B vitamins was seen to improve functional recovery of the nerve and muscular reinnervation. Administration of the combination of the vitamins thiamine, pyridoxine and cobalamin was superior to administration of the individual components.

In cold-induced nerve injury in the rat administration of vitamin B1, B6 and B12 significantly enhance the regenerative processes in the nerve.

In alloxan-induced diabetic neuropathy these B-vitamins also promote nerve regeneration. The model of streptozotocin-induced neuropathy demonstrates that the use of mixture of vitamins also counteracts a deterioration in functional properties such as nerve conduction velocity.

5.2 Pharmacokinetic properties

Thiamine

Vitamin B1 administered orally is assumed to have a dose-dependent dual transport mechanism, namely active absorption up to concentrations of 2 µmole and passive diffusion with concentrations over 2 µmole.

According to investigations using labelled thiamine absorption is greatest in the duodenal loop and occurs to a lesser extent in the upper and middle sections of the small intestine. There is virtually no absorption in the stomach and in distal sections of the small intestine. Thiamine synthesised by the flora of the colon is not absorbed. Absorption of thiamine takes place after phosphorylation in the epithelial cells; a carrier mechanism is assumed to be involved in passage through the intestinal wall. The fatsoluble thiamine derivatives are better absorbed than the water-soluble. Thiamine is excreted with a half-life of 1.0 hours for the beta-phase. The main excretion products are: thiamine carbonic acid, pyramine, thiamine and a number of metabolites not yet identified.

The greater the thiamine intake the more unchanged thiamine is excreted via the kidneys within 4 – 6 hours. The body stores approx. 30 mg. On account of the high turnover rate the reserve capacity (4 -10 days) is very limited.

Pyridoxine

Pyridoxine, pyridoxal and pyridoxamine are mainly rapidly absorbed in the upper gastrointestinal tract and are excreted with a maximum between 2 and 5 hours. The main excretion product is 4-pyridoxic acid. The function as a coenzyme depends on phosphorylation of the CH2-OH group at the 5 position (PALP). PALP is almost 80 % protein-bound in the blood. The body's vitamin B6 store amounts to between 40 and 150 mg, daily renal excretion amounts to 1.7 - 3.6 mg and the daily turnover rate is 2.2 to 2.4 %.

Cobalamin

Absorption of vitamin B12 from the gastrointestinal tract takes place by two mechanisms:

- The vitamin B12 taken up in the diet is released by the gastric acid and immediately bound to the intrinsic factor to form the actual vitamin B12 intrinsic factor complex
- Independently of the intrinsic factor vitamin B12 may passively enter the bloodstream by way of an unspecific mechanism.

According to studies in healthy persons a maximum of 1.5 µg of vitamin B12 administered orally is absorbed by way of the intrinsic factor. When the oral dose is increased, a saturation point is reached in the intrinsic factor-dependent uptake and there is an increase in diffusion-induced absorption of vitamin B12.

In patients with pernicious anaemia absorption rates of 1 % have been found after oral doses of 100 µg and over.

The vitamin B12 contained in the body is stored in depots, the liver being the most important of these. The vitamin B12 used up by the daily requirement is very low; it Neuro-B s.c.tabs SPC - MA Transfer - 5 - amounts to about 1 µg. The turnover rate is 2.5 µg B12 per dayor 0.05 % of the total stores in the body.

Vitamin B12 is mainly secreted in the bile and for the most part is reabsorbed via the enterohepatic circulation. If the storage capacity of the body is excreted by high doses of the vitamin, in particular in parenteral doses, the portion which is not retained is excreted in the urine.

The bioavailability of Neuro-B, Art. No. 304 (coated tablet) was investigated versus Neuro-B, Art. No. 302 (injection solution, i.m. administration).

Parenteral administration of the vitamin combination produces higher serum levels of the vitamin than oral administration. Use of parenteral vitamin B1, B6 and B12 formulations is therefore particularly appropriate at the start of therapy. In this connection it is necessary to consider the fact that in diabetics or alcoholics - who make up the larger part of patients with polyneuropathy - gastrointestinal disorders are often present which may also affect absorption of vitamins given orally.

There is no negative effect on the pharmacokinetic properties of the individual vitamins after combined administration of vitamin B1, B6 and B12.

5.3 Preclinical safety data

Thiamine

Very high intravenous doses of thiamine have a lethal effect in animal studies: mouse 125 mg/kg, rat 250 mg/kg, rabbit 300 mg/kg and dog 350 mg/kg (LD50).

In human very high intravenous doses (above 10 g) produce a ganglia-block, because thiamine is bound to nicotinic-cholinergic receptors.

Hypervitaminosis has not been described even after ingestion for several months.

Pyridoxine

Vitamin B6 has a relatively low toxicity. The acute toxicity of pyrodoxine hydrochloride is 6,000 mg/kg (oral) and 700 mg/kg (intravenous) in the mouse and 3,700 mg/kg (subcutaneous) in the rat (LD50). No chronic toxicity was found in the dog and the rat in a dosage of 20 and 25 mg/kg per day. Furthermore, no teratogenic effects were seen in the rat with a dosage of 80 mg/kg per day. Damage to the nervous system occurred in dogs given 1,000 mg vitamin B6 /kg per day for a period of several days.

Cobalamin

Vitamin B12 has a very low toxicity. The LD50 in the mouse is 1,600 mg (intraperitonial and intravenous).

The literature available does not present any findings indicating that vitamin B12 has cancerogenic or teratogenic properties.

Hypervitaminosis or poisoning induced by vitamin B12 are not known for humans

Combination of vitamins B1, B6 and B12

Findings are available from investigations with the combination of Vitamins B1, B6 and B12 from which it can be concluded that the fixed combination is tolerated and does not have a teratogenic effect either. The investigations were performed using Neuro-B injection solution (100 mg B1, 100 mg B6, 1 mg B12 per 3 ml).

Acute toxicity
Rat i.v. : LD50 = 3.51 mg/kg body weight. No late mortality.

Subacute toxicity
Rat i.m. : Daily intramuscular injection of 3 ml solution for 4 weeks was tolerated systemically.

Subacute toxicity
Beagle i.v. : No intolerance reactions with daily intravenous administration for 4 weeks of 0.1 ml, 0.3 ml, 1.0 ml and 3.0 ml/kg body weight.

Teratogenicity
Rabbit i.m. : No significant differences as compared to the control

group after daily administration of 0.3 ml, 1.0 ml and 3.0 ml/kg body weight from day 6 - day 18 of pregnancy.

Cancerogenicity : Not known to date.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate
Povidone K90
Sodium Starch Glycolate
Colloidal Silicon Dioxide
Magnesium Stearate
Hypromellose 15 cps
Triacetin
Talc
Titanium Dioxide

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30 °C

6.5 Nature and contents of container

Two Aluminum-Aluminum blisters of 10 tablets each, packed in a printed carton with folded leaflet.

6.6 Special precautions for disposal and other handling

Not Applicable

7. MARKETING AUTHORISATION HOLDER

Tabuk Pharmaceutical Manufacturing Company
Al-Madina Road, Tabuk, Kingdom of Saudi Arabia
P.O. Box 3633

8. MARKETING AUTHORISATION NUMBER

Neuro-B Film Coated Tablets
Marketing authorization number Ethiopia: **07807/08489/NMR/2020**

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF AUTHORISATION

Neuro-B Film Coated Tablets
Date of first authorization in Ethiopia: **23/09/2022**

10. DATE OF RIVISION

AUGUST 2023