

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Neurobion ampoules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

3 ml of aqueous solution (1 ampoule) contains:

Thiamine chloride hydrochloride (vitamin B ₁)	100 mg
Pyridoxine hydrochloride (vitamin B ₆)	100 mg
Cyanocobalamin (vitamin B ₁₂)	1 mg

Excipients: Contains 42 mg sodium per ampoule and traces of potassium.
For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection
Red, clear solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Neurological diseases caused by severe vitamin B₁, B₆ and B₁₂ deficiencies that cannot be remedied by means of oral therapy.

4.2 Posology and method of administration

For intramuscular administration.

Neurobion ampoules are to be administered intramuscularly (by deep intragluteal injection).

In severe (acute) cases: One ampoule daily until the acute symptoms subside.

After improvement of symptoms: One ampoule 1-3 times per week.

There is only limited experience with therapy in children and adolescents.

Neurobion coated tablets are recommended for supporting or continuing ongoing injection therapy and for relapse prophylaxis.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients.

4.4 Special warnings and special precautions for use

Neurobion ampoules must not be administered by intravenous injection.

Short-term parenteral vitamin B₁₂ administration may temporarily impair the diagnosis of funicular myelosis or pernicious anemia.

If symptoms of peripheral sensory neuropathy (paraesthesia) occur, the dosage should be reviewed and treatment with the medicinal product discontinued, if necessary. Neuropathies have been observed under long-term administration (over 6-12 months) of daily dosages exceeding 50 mg vitamin B₆ as well as in short-term administration (over 2 months) of more than 1 g vitamin B₆ per day.

Neurobion ampoules may be used in children and adolescents only in the case of compelling reasons.

Each ampoule contains 42 mg sodium. This is to be taken into account in persons under sodium-restricted diet (low in table salt/sodium).

Each ampoule contains traces of potassium.

4.5 Interaction with other medicinal products and other forms of interaction

Thiamine is inactivated by 5-fluorouracil as the latter competitively inhibits the phosphorylation of thiamine to thiamine pyrophosphate.

Loop diuretics, e.g. furosemide that inhibit tubular reabsorption may cause increased excretion of thiamine in long-term therapy and, thus, lowering of the thiamine level.

If taken simultaneously with L-dopa, vitamin B₆ can lessen the dopa effect.

The simultaneous administration of pyridoxine antagonists (e.g. isoniazide (INH), hydralazine, D-penicillamine or cycloserine) may increase the vitamin B₆ requirement.

Beverages containing sulphite (e.g. wine) enhance thiamine degradation.

4.6 Pregnancy and breastfeeding

Pregnancy

There are only insufficient animal studies on the effect of this medicinal product on pregnancy, embryo-foetal, prenatal and postnatal development. The possible risk for human beings is not known. The treating physician should decide about the use of this product during pregnancy after carefully weighing the risk-to-benefit ratio.

Lactation

Vitamins B₁, B₆ and B₁₂ are secreted into human breast milk. High concentrations of vitamin B₆ can inhibit the production of breast milk. Data on the extent of secretion into breast milk from animal studies are not available. Therefore, the advantages of breast-feeding for the infant should be carefully weighed against the therapeutic benefit for the women in order to decide to either discontinue breast-feeding or therapy with Neurobion.

4.7 Effects on ability to drive and use machines

Neurobion ampoules do not affect the capability to drive a vehicle or to operate machinery.

4.8 Undesirable effects

In the following, the undesirable effects are classified by organ system and frequency. The assessment of undesirable effects is based on the following frequency grouping:

Very common (1/10)

Common (1/100, <1/10)

Uncommon (1/1,000, <1/100)

Rare (1/10,000, < 1/1,000)

Very rare (< 1/10,000)

Unknown (frequency not estimatable on the basis of the data available)

Nervous system disorders:

Unknown: Long-term intake (> 6-12 months) of a daily dosage > 50 mg vitamin B₆ may cause peripheral sensory neuropathy.

Gastrointestinal disorders:

Unknown: Gastrointestinal complaints such as nausea, vomiting, diarrhoea and abdominal pain.

Immune system disorders:

Very rare: Hypersensitivity reactions such as sweating, tachycardia and skin reactions like itching and urticaria, as well as anaphylaxis.

Skin and subcutaneous tissue disorders:

Unknown: Allergic reactions, eczematous skin alterations and a benign form of acne have been observed after high-dose vitamin B₁₂.

General disorders and administration site conditions:

Unknown: Injection-site reactions.

4.9 Overdose

Vitamin B₁:

Thiamine has a broad therapeutic range. Very high doses (over 10 g) have a ganglion-blocking effect, similar to that of curare, and suppress the conduction of nerve impulses.

Vitamin B₆:

The toxic potential of vitamin B₆ can be considered as very low. Long-term treatment (> 6-12 months) of a daily dosage > 50 mg vitamin B₆ may, however, cause peripheral sensory neuropathy.

Continuous intake of vitamin B₆ at a daily dosage of more than 1 g over more than two months may produce neurotoxic effects.

Neuropathies with ataxia and sensitivity disorders, cerebral convulsions with EEG changes as well as, in individual cases, hypochromic anaemia and seborrhoeic dermatitis have been described after administration of more than 2 g daily.

Vitamin B₁₂:

Allergic reactions, eczematous skin alterations and a benign form of acne have been observed after high-dose parenteral administration.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vitamin B₁ in combination with vitamin B₆ and/or vitamin B₁₂

ATC Code: A11DB

Neurobion ampoules 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 balances deficiencies due to inadequate nutritive vitamin intake and thus ensures the availability of the required quantities of coenzymes.

Animal and clinical studies have indicated antinociceptive activity of vitamin B₁, B₆ and B₁₂.

5.2 Pharmacokinetic properties

Thiamine:

The elimination half-life is approx. 4 hours.

The human body can store approx. 30 mg thiamine. On account of the rapid metabolism, the reserve capacity, at 4-10 days, is very limited.

Pyridoxine:

Approx. 40 to 150 mg can be stored, 1.7 to 3.6 mg is excreted in the urine per day.

Cobalamin:

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. Vitamin B₁₂ is mainly secreted into bile and largely reabsorbed during the enterohepatic circulation.

5.3 Preclinical safety data

The toxicity of vitamins B₁, B₆ and B₁₂ is very low. The data available to date do not suggest any potential risk for humans.

The literature available on the subject does not contain any findings indicating that vitamins B₁, B₆ and B₁₂ have carcinogenic, mutagenic or teratogenic properties.

Chronic toxicity: In animals, very high doses of vitamin B₁ cause bradycardia. Other symptoms are blockade of vegetative ganglia and motor end plates. The oral administration of 150–200 mg of vitamin B₆/kg body weight/day over a period of 100–107 days caused ataxia, muscular asthenia, disorders of balance, as well as degenerative changes of axons and myelin sheaths in dogs. Animal studies also showed incidences of convulsions and impaired coordination after high doses of vitamin B₆.

Mutagenic and tumorigenic potential: Mutagenic effects of vitamin B₁ and vitamin B₆ are not to be expected under the conditions of clinical use. There are no long-term animal studies available on the tumorigenic potential of thiamine and vitamin B₆.

Reproduction toxicity: Thiamine is transported actively to the foetus. Concentrations in the foetus and the newborn exceed maternal concentrations of vitamin B₁. Systematic investigations on human embryonal and foetal development in connection with the use of vitamin B₁ at doses exceeding the stated daily requirements are not available.

Vitamin B₆ is insufficiently investigated in animal studies. An embryotoxicity study in rats gave no indications of a teratogenic potential. In male rats the administration of very high doses of vitamin B₆ induced damage to spermatogenesis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide (for pH adjustment)
Potassium cyanide
Water for injection

6.2 Incompatibilities

It is not recommended to use Neurobion ampoules together with other drugs in a 'mixed injection' or infusion.

Vitamin B₁ is completely degraded by sulphite-containing infusion solutions.

Other vitamins, especially cyanocobalamin, may be inactivated in the presence of vitamin B₁ degradation products.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the refrigerator (at 2°C to 8°C). Store the ampoules in the original carton to protect them from light.

6.5 Nature and contents of container

Amber glass ampoules (Type I) with 3 ml injection solution
Package sizes: 3 Ampules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other notes on handling

No specific notes.

7. MARKETING AUTHORIZATION HOLDER

Merck A.E.
41-45 Kifisias ave. (Building B')
15123 Marousi, Athens
Greece

8. MARKETING AUTHORIZATION NUMBER

795

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION

05/04/1971

10. DATE OF (PARTIAL) REVISION OF THE TEXT

07/08/2012

1. TRADE NAME OF THE MEDICINAL PRODUCT

Neurobion™ coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 coated tablet contains:

100 mg	Thiamine disulfide
200 mg	Pyridoxine hydrochloride
200 µg	Cyanocobalamin

3. PHARMACEUTICAL FORM

Coated tablet

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 column, 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 Contra-indications

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

4.4 Special warnings and special precautions for use

nil

4.5 Interaction with other medicaments and other forms of interaction

Patients treated with L-Dopa should not take high doses of pyridoxine (vitamin B₆) and thus not Neurobion, 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 lactation is not documented.

4.7 Effects on ability to drive and use machines

nil

4.8 Undesirable effects

In individual cases sweating, tachycardia, and skin reactions accompanied 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

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-oxoglutarate 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 non-oxidative metabolism of the amino acids. Through decarboxylation they are involved in the formation of physiologically active amines (e.g. adrenalin, histamine, serotonin, dopamine, tyramine) and through transamination 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 interactions take place with the remaining vitamins in the B complex. Animal studies indicate an antinociceptive effect from vitamin B₁₂.

Combination 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 fat-soluble 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 amounts to about 1 μg. The turnover rate is 2.5 μg B₁₂ per day or 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 exceeded 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 Neurobion, Art. No. 304 (coated tablet) was investigated versus Neurobion, 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 pyridoxine 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 (intraperitoneal 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 Neurobion 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

Magnesium stearate, Methylcellulose, Corn starch, Gelatin, Lactose monohydrate, Talc, Montan glycol wax, Acacia, Glycerol 85 %, Povidone 25, Calcium carbonate, Colloidal silicon dioxide, Kaolin, Titanium dioxide, Sucrose.

6.2 Incompatibilities

nil

6.3 Shelf-life

The stability of Neurobion coated tablets is 3 years.

6.4 Special precautions for storage

Do not store above 25° C.

6.5 Nature and contents of container

Packages with 20/100 tablets

6.6 Instructions for use/handling

nil

7. **MARKETING AUTHORIZATION HOLDER**

Merck A.E.
41-45 Kifisias ave. (Building B')
15123 Marousi, Athens
Greece

8. **MARKETING AUTHORIZATION NUMBER**

794

9. **DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION**

05.04.1971

10. **DATE OF (PARTIAL) REVISION OF THE TEXT**

22/06/2010