

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Neurobion coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One coated tablet contains:

Thiamine disulphide (vitamin B ₁)	100 mg
Pyridoxine hydrochloride (vitamin B ₆)	200 mg
Cyanocobalamin (vitamin B ₁₂)	200 µg

Excipients: Contains 133.22 mg sucrose.
For a complete list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Coated tablet
White, shiny, round, biconvex coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Neurological diseases caused by vitamin B deficiencies.

4.2 Posology and method of administration

Posology

One coated tablet once daily. In individual cases, the dose may be increased to one coated tablet 3 times daily.

The coated tablets are to be swallowed whole with plenty of liquid after meals.

Duration of administration

The physician in charge should decide on the duration of administration.

After a maximum period of four weeks, it should be decided whether to reduce the dose. (See section 4.4 'Special warnings and precautions for use')

Paediatric population

Neurobion coated tablets must not be used in children and adolescents (< 18 years).

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Neurobion coated tablets must not be used in children and adolescents due to their high active substance content.

4.4 Special warnings and precautions for use

The clinical picture as well as the laboratory parameters of funicular myelosis or of pernicious anaemia can lose specificity by administration of vitamin B₁₂.

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 intake (over 6-12 months) of daily dosages exceeding 50 mg vitamin B₆ as well as in short-term intake (over 2 months) of more than 1 g vitamin B₆ per day. Therefore, regular monitoring is recommended under long-term treatment.

This drug contains sucrose; therefore its use is not recommended in patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency.

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.

Antacids diminish the absorption of thiamine.

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 serum 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 decrease the efficacy of vitamin B₆ (pyridoxine).

Long term use of acid-lowering agents may lead to vitamin B₁₂ deficiency.

Alcohol and black tea diminish the absorption of thiamine.

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

4.6 Fertility , pregnancy and lactation

Pregnancy

During pregnancy and the nursing period the generally recommended daily dosage of vitamin B₁ is 1.4 mg and of vitamin B₆ 1.9 mg.

These dosages may be exceeded in pregnant patients with manifest vitamin B₁ and B₆ deficiencies only as the safety of doses higher than the recommended daily dosage has not yet been demonstrated. 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.

Breast-feeding Vitamins B₁, B₆ and B₁₂ are secreted into human breast milk. High concentrations of vitamin B₆ i.e. > 600 mg daily, 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 coated tablets 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 ($\geq 1/10$)

Common ($\geq 1/100$, to $< 1/10$)

Uncommon ($\geq 1/1.000$, to $< 1/100$)

Rare ($\geq 1/10.000$, to $< 1/1.000$)

Very rare ($< 1/10.000$),

Not known (frequency cannot be estimated from the available data)

Nervous system disorders:

Not known: 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.

Renal and urinary disorders:

Not known: Chromaturia (“reddish urine”, appeared during the first 8 hours after an administration and typically resolves within 48 hours).

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions is an important way to gather more information to continuously monitor the benefit/risk balance of the medicinal product. Any suspected adverse reactions should be reported to Pharmaceutical Services, Ministry of Health, CY-1475, www.moh.gov.cy/phs Fax: + 357 22608649

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 intake (> 6 - 12 months) of a daily dosage > 50 mg vitamin B₆ may, however, cause peripheral sensory neuropathy and other sensorial neuropathy syndromes. These symptoms improve gradually upon vitamin discontinuation..

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 changes and a benign form of acne have been observed after high parenteral doses (in rare cases also after oral doses).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Neurobion coated tablets 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 may supplement inadequate nutritive vitamin intake and thus ensure the availability of the required quantities of coenzymes.

The therapeutic use of these vitamins in diseases of the nervous system serves, on the one hand, to compensate for concomitant deficiencies (possibly due to an increased requirement induced by the disease) and, on the other, to stimulate natural repair mechanisms.

Thiamine (vitamin B₁)

Thiamine pyrophosphate (TPP) is the effective form of vitamin B₁ and acts as a coenzyme for a number of enzymes (e.g. pyruvate dehydrogenase and transketolase). Accordingly, vitamin B₁ is primarily involved in the carbohydrate metabolism; however, it also intervenes in the synthesis of lipids and amino acids. Nerve cells cover their energy requirement exclusively via enzymatic oxidation and decarboxylation of glucose, so that an adequate supply of vitamin B₁ is of crucial importance. Thiamine is also involved in the conduction of nerve impulses.

Models used in animal studies have indicated analgetic activity for vitamin B₁.

Manifestations of vitamin B₁ deficiency are very multifaceted and can involve central and peripheral nervous system, the cardiovascular system, skin and other body systems. Specific symptoms can include polyneuropathy with paraesthesia (tingling, burning, numbness), hyperaesthesia (increased sensitivity), muscle weakness, altered temperature sensitivity, oedema, and others.

Pyridoxine (vitamin B₆)

Pyridoxal phosphate, the biologically active form of pyridoxine, is the determinative coenzyme in amino acid metabolism. It is involved in the formation of physiologically active amines (e.g. serotonin, histamine, adrenalin) through decarboxylation processes, as well as in anabolic and catabolic processes through transamination.

Pyridoxal phosphate plays an essential role in the nervous system, especially in the enzymatically controlled neurotransmitter metabolism. As a catalyst of the first biosynthesis steps of sphingosine, pyridoxal phosphate also has a key role in the metabolism of sphingolipids. Sphingolipids are essential constituents of the myelin sheaths of nerve cells. Animal experimental models have demonstrated that vitamin B₆ has an analgesic effect.

Vitamin B₆ deficiency can be associated with peripheral neuritis and neuropathy, paresthesia, burning, painful dysesthesia, disorders of oxalate metabolism, depression of immune responses, anemia, lesions of the mucous membranes and other symptoms.

Cobalamin (vitamin B₁₂)

Vitamin B₁₂ in its coenzyme forms (5-deoxyadenosyl cobalamin and methyl cobalamin) is involved in enzymatically catalysed intramolecular hydrogen displacements and in intramolecular transfers of methyl groups. Vitamin B₁₂ is also involved in methionine synthesis (closely coupled to the synthesis of nucleic acids) and in lipid metabolism, via the conversion of propionic acid into succinic acid. Vitamin B₁₂ is involved in the methylation of the myelin basic protein, a constituent of the myelin sheaths of the nervous system. Methylation increases the lipophilic properties of the myelin basic protein, which favours increased integration in the myelin sheaths.

Vitamin B₁₂ deficiency can result in neurological symptoms like paresthesia, numbness, gait impairment, impaired vibration sense, polyneuritis (particularly sensory, in the distal extremities), ataxia and others. Further symptoms can be anaemia, optic atrophy, altered mental status and others.

Combination of vitamins B1, B6 and B12

Neurotropic vitamins B1, B6 and B12 alone, and in combination as the result of biochemical synergy, have special significance for the metabolism of the nervous system, which justifies their combined use.

Further, in most of the patient populations such as elderly, diabetic patients and others, deficiency of all three neurotropic vitamins is present.

Animal studies have shown that this combination of neurotropic B vitamins accelerates regenerative processes in damaged nerve fibres, which finally leads to enhanced restoration of function and muscle innervation. In the model of experimental diabetes in rats, administration of B complex vitamins prevented or attenuated the characteristic nerve damage, so that deterioration of the functional properties was counteracted (antineuropathic effect).

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

5.2 Pharmacokinetic properties

Combined administration of vitamins B1, B6 and B12 is not expected to have a negative effect on the pharmacokinetics of the individual vitamins.

Thiamine(vitamin B1) :

Has after oral administration a dose-dependent dual transport mechanism:

Active absorption up to concentrations of 2 μmol and passive diffusion in concentrations over 2 μmol).

There is almost no absorption in the stomach and in distal segments of the small intestine. Thiamine formed by the large intestinal flora is not absorbed. Absorption of thiamine takes place after phosphorylation in the epithelial cells; a carrier mechanism is assumed to be involved in the passage through the intestinal wall.

After absorption by the intestinal mucosa, thiamine is transported to the liver via the portal circulation. In the liver, thiamine is phosphorylated to thiamine pyrophosphate (TPP) and thiamine triphosphate (TTP) by means of thiamine kinase.

The biological half-life of thiamine in humans is about 9.5 to 18.5 days, with an 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(vitamin B6):

Pyridoxine is absorbed very rapidly, mainly in the upper gastrointestinal tract, and is excreted with a maximum between 2 and 5 hours.

Vitamins are bound to albumin. Vitamin B6 passes into the spinal fluid, is secreted into breast milk, and permeates the placenta. The principal excretion product is 4-pyridoxic acid; the amount of the latter depending on the vitamin B6 dose taken up.

Vitamin B6 is phosphorylated mainly in the liver, forming the biologically active pyridoxal phosphate. To cross cell membranes, phosphorylated vitamin B6 must be hydrolysed by alkaline phosphatase to free vitamin B6. Transport into the cells is by simple diffusion followed by rephosphorylation, and a specialized intestinal carrier-mediated system for pyridoxine uptake has been discussed recently. Peak concentrations are reached after 3.5 to 4 hours. The biological half-life of pyridoxal phosphate is about 15 - 25 days. The storage capacity for vitamin B6 is 14 to 42 days.

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

Cobalamin (vitamin B12):

Cobalamin is absorbed from the gastrointestinal tract by means of 2 mechanisms:

- release through gastric acid and immediate binding to the intrinsic factor. A maximum of 1.5-2 μg of oral vitamin B12 is absorbed via this mechanism
- independently of the intrinsic factor through passive influx in the blood

At doses over 1.5 µg the latter mechanism increases in significance.
Patients with pernicious anaemia absorb approx. 1% of oral doses of 100 µg and over.
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. The biological half-life is about 1 year.
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

Tablet core:

Magnesium stearate,
Methyl cellulose,
sodium starch glycolate Gelatin,
mannitol Talc,
Glycerol 85 %, colloidal anhydrous silica, purified water

Tablet coating:

Montan-glycol wax,
Gelatin,
Methyl cellulose,
Acacia,
Glycerol 85 %,
Povidone,
Calcium carbonate,
Colloidal anhydrous silica,
Kaolin,

Titanium dioxide (E 171),
Talc,
Sucrose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

PVC foil coated with PVDC (40 g/ m²)
Aluminum Foil
Water based print primer lacquer outside

Package sizes: 20 coated tablets

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

P&G Health Germany GmbH
Sulzbacher Strasse 40
65824 Schwalbach am Taunus
Germany

8. MARKETING AUTHORISATION NUMBER

794

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05.04.1971

10. DATE OF REVISION OF THE TEXT:

27.04.20

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

Posology

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

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

Paediatric population

Neurobion ampoules are contraindicated in children below 14 years (see section 4.3).

Method of administration

For intramuscular administration.

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

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 listed in section 6.1.
- children below the age of 14 years (due to the high doses of the active ingredients)

4.4 Special warnings and 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. Therefore, regular monitoring is recommended under long-term treatment.

-Neurobion ampoules must not be used in children below the age of 14 years (due to their high active substance content).

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 serum 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 decrease the efficacy of vitamin B₆ (pyridoxine).

Long term use of acid-lowering agents may lead to vitamin B₁₂ deficiency.

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

4.6 Fertility, pregnancy and lactation

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.

Breast-feeding

Vitamins B₁, B₆ and B₁₂ are secreted into human breast milk. High concentrations of vitamin B₆, i.e. > 600 mg daily, 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 ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

Rare ($\geq 1/10,000$ to $< 1/1,000$)

Very rare ($< 1/10,000$)

Not known (frequency cannot be estimated from the available data)

Nervous system disorders:

Not known: Long-term intake (> 6-12 months) of a daily dosage > 50 mg vitamin B₆ may cause peripheral sensory neuropathy.

Gastrointestinal disorders:

Not known: 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:

Not known: Allergic reactions, eczematous skin alterations and a benign form of acne have been observed after high-dose vitamin B₁₂.

Renal and urinary disorders:

Not known: Chromaturia ("reddish urine", appeared during the first 8 hours after an administration and typically resolves within 48 hours).

General disorders and administration site conditions:

Not known: Injection-site reactions.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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

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. These symptoms improve gradually upon vitamin discontinuation.

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.

Thiamine (vitamin B₁)

Thiamine pyrophosphate (TPP) is the effective form of vitamin B₁ and acts as a coenzyme for a number of enzymes (e.g. pyruvate dehydrogenase and transketolase). Accordingly, vitamin B₁ is primarily involved in the carbohydrate metabolism; however, it also intervenes in the synthesis of lipids and amino acids. Nerve cells cover their energy requirement exclusively via enzymatic oxidation and decarboxylation of glucose, so that an adequate supply of vitamin B₁ is of crucial importance. Thiamine is also involved in the conduction of nerve impulses. Furthermore, results obtained in experiments indicate an analgesic effect.

Manifestations of vitamin B1 deficiency are very multifaceted and can involve the central and peripheral nervous system, the cardiovascular system, the skin and other body systems. Specific symptoms can include polyneuropathy with paraesthesia (tingling, burning, numbness), hyperesthesia (increased sensitivity), muscle weakness, altered temperature sensitivity, oedema, and others.

Pyridoxine (vitamin B6)

Pyridoxal phosphate, the biologically active form of pyridoxine, is the determinative coenzyme in amino acid metabolism. It is involved in the formation of physiologically active amines (e.g. serotonin, histamine, adrenalin) through decarboxylation processes, as well as in anabolic and catabolic processes through transamination.

Pyridoxal phosphate plays an essential role in the nervous system, especially in the enzymatically controlled neurotransmitter metabolism. As a catalyst of the first biosynthesis steps of sphingosine, pyridoxal phosphate also has a key role in the metabolism of sphingolipids. Sphingolipids are essential constituents of the myelin sheaths of nerve cells. Animal experimental models have demonstrated that vitamin B6 has an analgesic effect. Vitamin B6 deficiency can be associated with peripheral neuritis and neuropathy, paresthesia, burning, painful dysesthesia, disorders of oxalate metabolism, depression of immune responses, anemia, lesions of the mucous membranes and other symptoms.

Cobalamin (vitamin B12)

Vitamin B12 in its coenzyme forms (5-deoxyadenosyl cobalamin and methyl cobalamin) is involved in enzymatically catalysed intramolecular hydrogen displacements and in intramolecular transfers of methyl groups. Vitamin B12 is also involved in methionine synthesis (closely coupled to the synthesis of nucleic acids) and in lipid metabolism, via the conversion of propionic acid into succinic acid.

Vitamin B12 is involved in the methylation of the myelin basic protein, a constituent of the myelin sheaths of the nervous system. Methylation increases the lipophilic properties of the myelin basic protein, which favours increased integration in the myelin sheaths.

Vitamin B12 deficiency can result in neurological symptoms like paresthesia, numbness, gait impairment, impaired vibration sense, polyneuritis (particularly sensory, in the distal extremities), ataxia and others. Further symptoms can be anaemia, optic atrophy, altered mental status and others.

Combination of vitamins B1, B6, and B12

Neurotropic vitamins B1, B6 and B12 alone, and in combination as the result of biochemical synergy, have special significance for the metabolism of the nervous system, which justifies their combined use.

Further, in most of the patient populations such as elderly, diabetic patients and others, deficiency of all three neurotropic vitamins is present.

Animal studies have shown that this combination of neurotropic B vitamins accelerates regenerative processes in damaged nerve fibres, which finally leads to enhanced restoration of function and muscle innervation. In the model of experimental diabetes in rats, administration of B complex vitamins prevented or attenuated the characteristic nerve damage, so that deterioration of the functional properties was counteracted (antineuropathic effect).

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

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

5.2 Pharmacokinetic properties

Combined administration of vitamins B1, B6 and B12 is not expected to have a negative effect on the pharmacokinetics of the individual vitamins.

Thiamine (vitamin B1):

The biological half-life of thiamine in humans is about 9.5 to 18.5 days, with an elimination half-life of approx. 4 hours.

The reserve capacity is 4-10 days. The high turnover rate and limited storage of thiamine (20-30 mg, mainly in the heart, brain, liver, and kidneys) require an adequate daily thiamine intake to meet requirements. Deficiency can present within 2-3 weeks of intake ceasing. Typical symptoms are tiredness, nausea, vomiting, obstipation, headache, tachycardia, and weak muscle reflexes.

Pyridoxine (vitamin B6):

Vitamin B6 is phosphorylated mainly in the liver, forming the biologically active pyridoxal phosphate. To cross cell membranes, phosphorylated vitamin B6 must be hydrolysed by alkaline phosphatase to free vitamin B6. Transport into the cells is by simple diffusion followed by rephosphorylation. Peak concentrations are reached after 3.5 to 4 hours. The biological half-life of pyridoxal phosphate is about 15 - 25 days with an elimination half-life of approximately 3 hours. The storage capacity for vitamin B6 is 14 to 42 days. Approx. 40 to 150 mg can be stored, 1.7 to 3.6 mg is excreted in the urine per day.

Cobalamin (vitamin B12):

Oral vitamin B12 is known to have a low absorption rate which may be further decreased, following bariatric surgery, in elderly patients, dialysis patients and patients with other conditions of malabsorption. Apart from saturable active absorption of oral vitamin B12, leading to daily absorption of approximately 1.5µg, vitamin B12 is also absorbed by passive diffusion. The proportion absorbed by passive diffusion is only approximately 1% of the ingested quantity. This is further reduced in patients who have had bariatric surgery or have an impaired gastrointestinal absorption due to other diseases. In these patients, parenteral application may be indicated.

About 90% of plasma cobalamin is bound to proteins (transcobalamins). Most of the Vitamin B12 not circulating in the plasma 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 excreted via the bile and largely reabsorbed during the enterohepatic circulation. If the body's storage capacity is exceeded as a result of high-dose and, in particular, parenteral administration, the portion not retained is excreted in the urine.

Results of pharmacokinetic studies using parenteral vitamin B preparations suggest that intramuscular and intravenous B-vitamins lead to higher cyanocobalamin plasma levels than high oral doses. In addition, parenteral and oral preparations of vitamins B1, B6 and B12 are equally well tolerated. Consequently, parenteral application of vitamins B1, B6 and B12 may be adequate for rapid restoration of vitamin stores in acute deficiencies and in patients with vitamin B absorption problems and in patients with an increased need due to certain pathological conditions.

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

Do not re-use syringes and needles. Syringes and needles must be disposed immediately after use.

Used syringes and needles must not be disposed in waste bins or toilets, but they must be disposed in a special sharps container.

7. MARKETING AUTHORIZATION HOLDER

P&G Health Germany GmbH
Sulzbacher Strasse 40
65824 Schwalbach am Taunus
Germany

8. MARKETING AUTHORIZATION NUMBER

795

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION

05/04/1971

10. DATE OF (PARTIAL) REVISION OF THE TEXT

13 April 2020