

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Neurobion Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Thiamine hydrochloride	100 mg
Pyridoxine hydrochloride	100 mg
Cyanocobalamin	1 mg

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Solution for injection.

Clear red sterile solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Adjuvant therapy in the management of peripheral neuropathy related to vitamin B complex deficiency.

4.2 Posology and method of administration

For administration by slow, deep intramuscular injection. One ampoule daily until the acute symptoms resolve. One ampoule two or three times a week as treatment maintenance.

4.3 Contraindications

Known hypersensitivity to any of the active ingredients.

4.4 Special warnings and special precautions for use

The content of pyridoxine may interfere with the effects of concurrent levodopa therapy.

Very rarely hypersensitivity reactions to vitamin B₁ injection have been reported. These reactions are usually associated with intravenous administration and, unless otherwise indicated the intramuscular route is to be preferred.

Mild allergic reactions such as sneezing or mild asthma are warning signs that further injections may give rise to anaphylactic shock.

4.5 Interaction with other medicinal products and other forms of interaction

Patients treated with L-dopa should not take high doses of pyridoxine and thus Neurobion, as pyridoxine attenuates the effect of L-dopa.

4.6 Pregnancy and lactation

Neurobion should not be used during pregnancy unless considered essential by a physician.

There is no information on whether the administration of these vitamins leads to elevated levels in breast milk, therefore Neurobion should not be administered to women nursing infants.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Vitamin B₁: In individual cases hypersensitivity reactions e.g. sweating, tachycardia, skin reactions with pruritus and urticaria have been reported. After parenteral administration of vitamin B₁ exanthemas, difficulties in breathing and conditions of shock may occur.

Vitamin B₆: With the recommended dose no adverse effects have been reported.

Vitamin B₁₂: After parenteral administration of vitamin B₁₂, acne, eczematous and urticaria like reactions have been reported.

4.9 Overdose

The vitamins B₁, B₆ and B₁₂ have a wide therapeutic range. With the recommended usage, no symptoms of overdose have been recorded.

Extremely high doses of vitamin B₁ (>10g) show a curare like effect. The toxic potential of the vitamins B₆ and B₁₂ is very low.

Sensory neuropathy at daily doses exceeding 500mg of pyridoxine has been reported, however, daily treatment doses of 250-500mg has not reduced the measured nerve conduction velocity.

Any sign of intoxication should be treated symptomatically.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Thiamine (Vitamin B₁)

Thiamine is phosphorylated in the body to biologically active thiamine pyrophosphate (TPP) and thiamine triphosphate (TTP). TPP is an important coenzyme in carbohydrate metabolism, especially important in nerve cells, e.g. it is the coenzyme for pyruvate decarboxylase, 2-oxoglutamate dehydrogenase and transketolase. It is also involved in the pentose phosphate cycle with the transfer of aldehyde groups and it catalyses the formation of acetylcholine.

Pyridoxine (Vitamin B₆)

In its phosphorylated form (pyridoxal-5-phosphate, PALP), pyridoxine is the coenzyme of a large number of enzymes including the non-oxidative metabolism of the amino acids. Decarboxylation, for example, results 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. glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase, gamma-amino butyric acid, α -ketoglutaric transaminase).

Cobalamin (Vitamin B₁₂)

Vitamin B₁₂ is an essential active principle for humans and important for the synthesis of the nucleic acids RNA and DNA and the synthesis of protein and lipids in the cell. The cyanocobalamin taken up as a pro-drug must first of all be

converted to the coenzymes methyl cobalamin 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 which is important for erythropoiesis. 5-desoxyadenosyl cobalamin is required for the formation of succinyl coenzyme A which is necessary for the formation of normal fatty acid chains.

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.

The effect of the combination on the regeneration of nerves has been examined and after experimentally induced nerve lesion and injury 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.

5.2 Pharmacokinetic properties

Thiamine

Thiamine is excreted with a half-life of 1.0 hours for the β -phase. It is mainly excreted as metabolites but the greater the thiamine intake the more unchanged thiamine is excreted via the kidneys within 4-6 hours. The body stores approx. 30mg. On account of the high turnover rate the reserve capacity (4-10 days) is very limited.

Pyridoxine

Pyridoxine is eliminated rapidly, with the main excretion product being 4-pyridoxic acid. The phosphorylated coenzyme is almost 80% protein-bound in the blood. The body's vitamin B₆ store amounts to between 40 and 150mg, daily renal excretion amounts to 1.7 - 3.6 mg and the daily turnover rate is 2.2 to 2.4%.

Cobalamin

The vitamin B₁₂ contained in the body is stored in depots, the liver being the most important of these. The vitamin B₁₂ used by the daily requirement is very low; it amounts to about 1 μ g. The turnover rate is 2.5 μ g B₁₂ per day or 0.05% of the total stores in the body.

Vitamin B₁₂ is secreted in the bile and mostly 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.

5.3 Preclinical safety data

The parenteral LD₅₀ values for thiamine, pyridoxine and cobalamin in mice are 125, 700 and 1600 mg/kg respectively. From the data available, there is no indication of an effect on the foetus or reproduction, or of a carcinogenic effect.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Potassium cyanide
Benzyl alcohol
Sodium hydroxide solution
Water for injections

6.2 Incompatibilities

Neurobion injection solution should not be mixed with other medicaments within a syringe or infusion.

Vitamin B₁ will be fully decomposed by solutions containing sulfite-compounds.

Other vitamins, especially cyanocobalamin, may be inactivated by decomposition products of vitamin B₁.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Store in refrigerator (2-8°C).

6.5 Nature and contents of container

3ml amber glass ampoules.

Pack size: 3 ampoules.

6.6 Instructions for use and handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Merck Limited
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8 MARKETING AUTHORISATION NUMBER

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