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 B₁)  100 mg
Pyridoxine hydrochloride (vitamin B₆)        100 mg
Cyanocobalamin (vitamin B₁₂)                 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
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 B₁) 100 mg
- Pyridoxine hydrochloride (vitamin B₆) 200 mg
- Cyanocobalamin (vitamin B₁₂) 200 µg

Excipients: Contains 40 mg lactose monohydrate and 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

Dosage
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’)

Children and adolescents
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.
- Neurobion coated tablets must not be used in children and adolescents due to their high active substance content.
4.4 Special warnings and special 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 B\textsubscript{12}.

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 B\textsubscript{6} as well as in short-term intake (over 2 months) of more than 1 g vitamin B\textsubscript{6} per day.

This drug contains lactose monohydrate and sucrose. Patients with rare, inherited fructose-galactose intolerance, Lapp lactase deficiency, glucose-galactose malabsorption, or sucrase-isomaltase deficiency should not take Neurobion coated tablets.

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 level.

If taken simultaneously with L-dopa, vitamin B\textsubscript{6} can lessen the dopa effect.

The simultaneous administration of pyridoxine antagonists (e.g. isoniazide (INH), hydralazine, D-penicillamine or cycloserine) may increase the vitamin B\textsubscript{6} requirement.

Alcohol and black tea diminish the absorption of thiamine.

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

4.6 Pregnancy and breastfeeding

Pregnancy
During pregnancy and the nursing period the generally recommended daily dosage of vitamin B\textsubscript{1} is 1.4 mg and of vitamin B\textsubscript{6} 1.9 mg.
These dosages may be exceeded in pregnant patients with manifest vitamin B\textsubscript{1} and B\textsubscript{6} 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.

Nursing period
Vitamins B\textsubscript{1}, B\textsubscript{6} and B\textsubscript{12} are secreted into human breast milk. High concentrations of vitamin B\textsubscript{6} 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 (≥1/10)
- Common (≥1/100, <1/10)
- Uncommon (≥1/1,000, <1/00)
- 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.

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.

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.

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

5.2 Pharmacokinetic properties

Thiamine:
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.
The elimination half-life is approx. 4 hours.
The human body can store approx. 30 mg thiamine. On account of the rapid metabolisation, the reserve capacity, at 4-10 days, is very limited.

Pyridoxine:
Pyridoxine is absorbed very rapidly, mainly in the upper gastrointestinal tract, and is excreted with a maximum between 2 and 5 hours.
Approx. 40 to 150 mg can be stored, 1.7 to 3.6 mg is excreted in the urine per day.

Cobalamin:
Cobalamin is absorbed from the gastrointestinal tract by means of 2 mechanisms:
- release through gastric acid and immediate binding to the intrinsic factor
- 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.
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
- Corn starch
- Gelatin
- Lactose monohydrate
- Talc

**Tablet coating:**
- Montan-glycol wax
- Gelatin
- Methylcellulose
- Acacia
- Glycerol
- Povidone
- Calcium carbonate
- Colloidal silicon dioxide
- Kaolin
- Titanium dioxide (E 171)
- Sucrose
6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Blister pack consisting of base film (hard PVC, transparent, coated with PVDC) and cover foil (aluminium foil coated with heat-sealing lacquer).

Package sizes: 20 coated tablets

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER

794

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05.04.1971