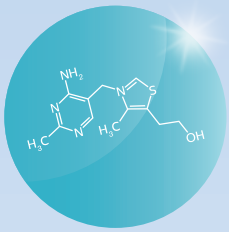
Neurobion®
VITAMIN B1, B6, B12

The neuropathy expert

Diabetic peripheral neuropathy

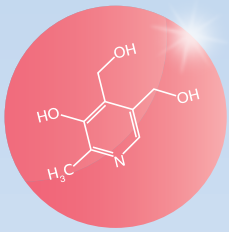
Neurotropic B vitamins as a treatment for peripheral neuropathy, including painful symptoms

Neurotropic vitamins B1, B6 and B12 improve the health of the nervous system via different modes of action, complementing each other to develop a synergistic beneficial effect, providing relief of the typical neuropathic symptoms.



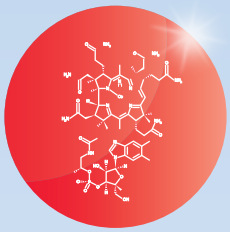
Vitamin B1

Involved in energy metabolism, nerve stimulation, modulator of neuronal and neuro-muscular transmission, neurotransmitter turnover and synthesis, lipid incorporation into myelin.[10,11] May prevent cell damage due to hyperglycemia.[11]



Vitamin B6

Involved in neurotransmitter synthesis, amino acid and homocysteine metabolism, glucose and lipid metabolism, DNA/RNA synthesis.[12]



Vitamin B12

Involved in myelinisation and remyelinisation, formation of myelin sheaths, neural differentiation.[13-15]

Treatment with Neurobion – Patient Journey

Neuropathy | **Asymptomatic** | **Mild** | **Moderate** | **Severe**

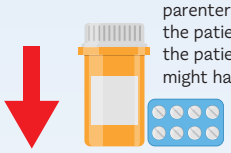
Treatment should be started with a higher dose to make sure the stores are filled as soon as possible.

Asymptomatic
B deficiency; assessment of the B vitamins need is done based on risk factors or B vitamin levels.

Mild to moderate symptoms of B deficiency; presence of risk factors and/or decreased B vitamin levels*

Severe symptoms of B deficiency; presence of risk factors and/or low B vitamin levels.

Physician can decide whether oral or parenteral application is most suitable for the patient depending on the condition of the patient and product availability; patient might have a preference **



STOP

High dose oral application of B vitamins (Neurobion tab 3/day for 4-12 weeks, depending on onset of effect and severity of the deficiency)

High dose parenteral application of B vitamins

Symptoms get better, switch to maintenance treatment.

Symptoms get better, switch to maintenance treatment.

CONTROL

Maintenance treatment with pharmacological dose of B vitamins (B1, B6 and B12) Neurobion tab. After 6-12 months to be monitored by a physician due to possible side effects of vitamin B6. Treatment duration depends on the cause of B deficiency.

*For specific patient groups parenteral treatment is preferred e.g. hospitalized patients, elderly, patients with severe absorption issues due to GI diseases, etc. Physician decides.
**Oral application of high dose of vitamin B12 is as effective as parenteral application to restore B12 levels. Posology and duration differs. Some patient groups still require parenteral application, physician decides.
Disclaimer: The patient journey is for reference purposes only. Management should be basing on patient's individualized condition as decided by treating physician.

Susan, 59 years, critical care nurse

- Known type 2 diabetes for 12 years, treated with metformin.
- Reported a gradual and symmetric loss of sensation in her feet over the last 2 years.
- Examination confirmed complete loss of touch sensation, vibration sensation, proprioception.
- Reflex tests showed a reduced ankle jerk reflex.

Diabetic Peripheral Neuropathy can show in many ways

Watch out for possible symptoms of nerve malfunction.

Distribution and development[1-3]
Sensory symptoms are symmetric and start in the toes, then affect upper limbs in a stocking-glove distribution. They usually develop gradually over years. Motor involvement is not typical for early stages.

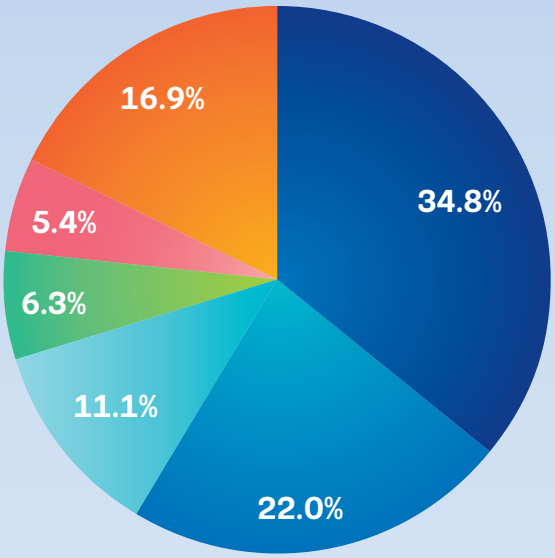
Range of sensory symptoms[1,2,4]
loss of pain sensation/insensitivity, tingling, "pins and needles" sensation, burning, "electric shocks", allodynia, hyperalgesia often worse at night. Numbness AND sensitivity can occur simultaneously.

Other symptoms of nerve damage[2]
Nerve damage can affect all nerves and thereby all body systems. Symptoms vary and may include difficulty swallowing, slowed digestion, dysesthesia, diarrhea, urinary incontinence, facial, mouth and eyelid drooping, vision changes, dizziness, muscle weakness, and others.

No predictor of axonal loss[1]
Symptoms are not a predictable indicator of severity of axonal loss.

Diabetes is the most common reason for peripheral neuropathy

In more than a third of patients with peripheral neuropathy the cause is diabetes.[5]



Etiology of polyneuropathies[5]

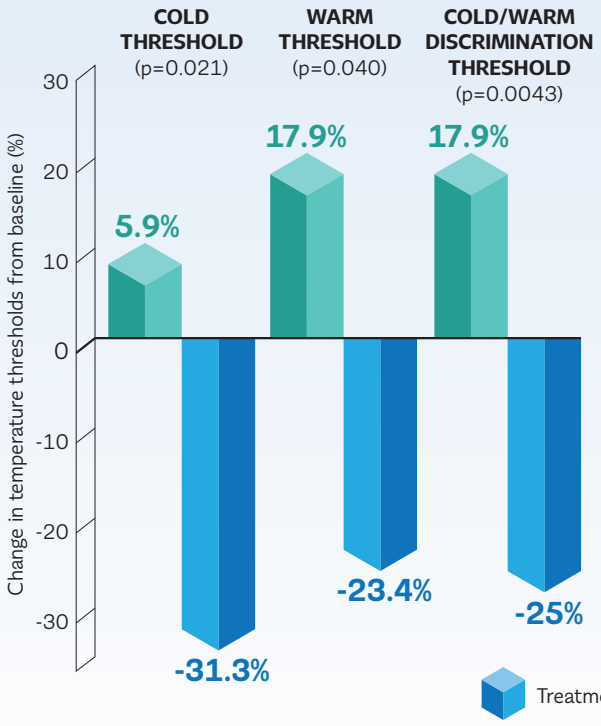
- Peripheral neuropathy is a complication in ≥ 50% of diabetes patients.[2,5]
- **Prevalence increases** with "diabetes years"
- 8% of diabetics have neuropathy at the time of diabetes diagnosis and 50% after 25 years of diabetes.[6]
- In up to 50% of patients diabetic peripheral neuropathy may be asymptomatic.[2]

Diabetes mellitus
Unclear etiology
Alcohol
Guillan-Barré-Syndrome
Infections
Others*

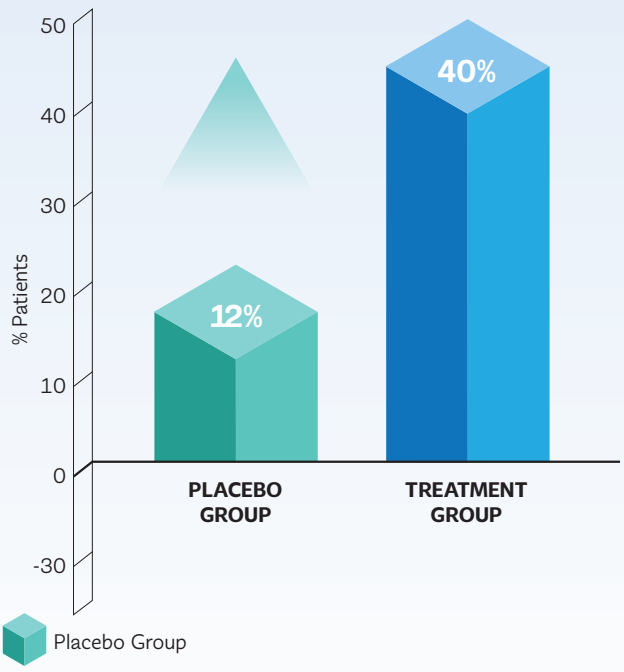
*Most common in "others" = vasculitis, chronic inflammatory demyelinating polyneuropathy, malabsorption, paraneoplastic, hereditary polyneuropathies, paraproteinaemia, toxins (excl. alcohol), amyloidosis.

Neurobion is proven to promote nerve health by regenerating nerves[8]

Neurobion® decreased temperature discrimination thresholds in the upper extremities after 18 weeks (n=33).

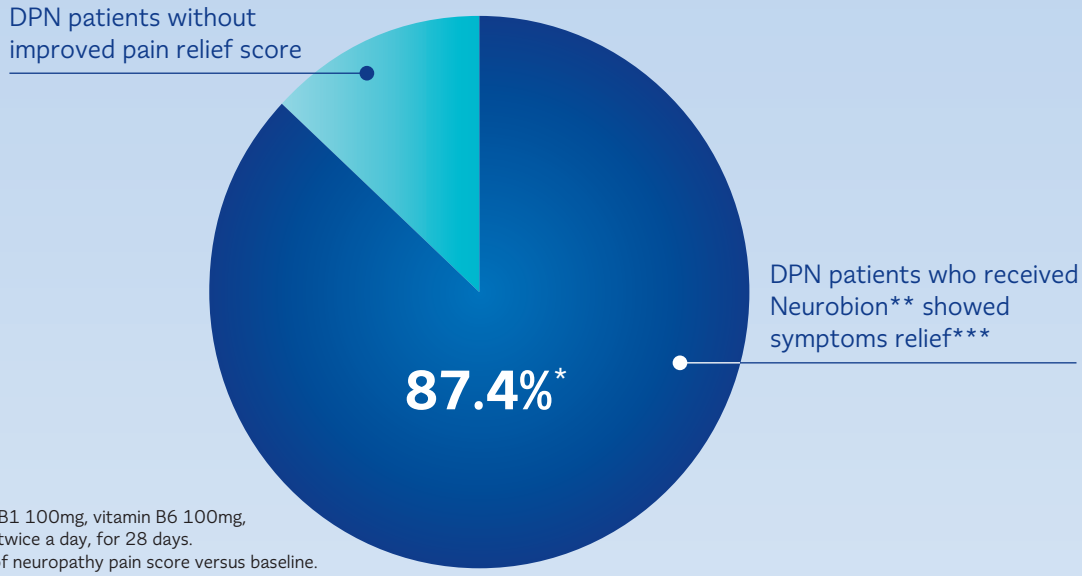


Painful small fiber neuropathy in the lower extremities improved with Neurobion® after 18 weeks of therapy as well as a further 8 weeks of washout period (n=33).



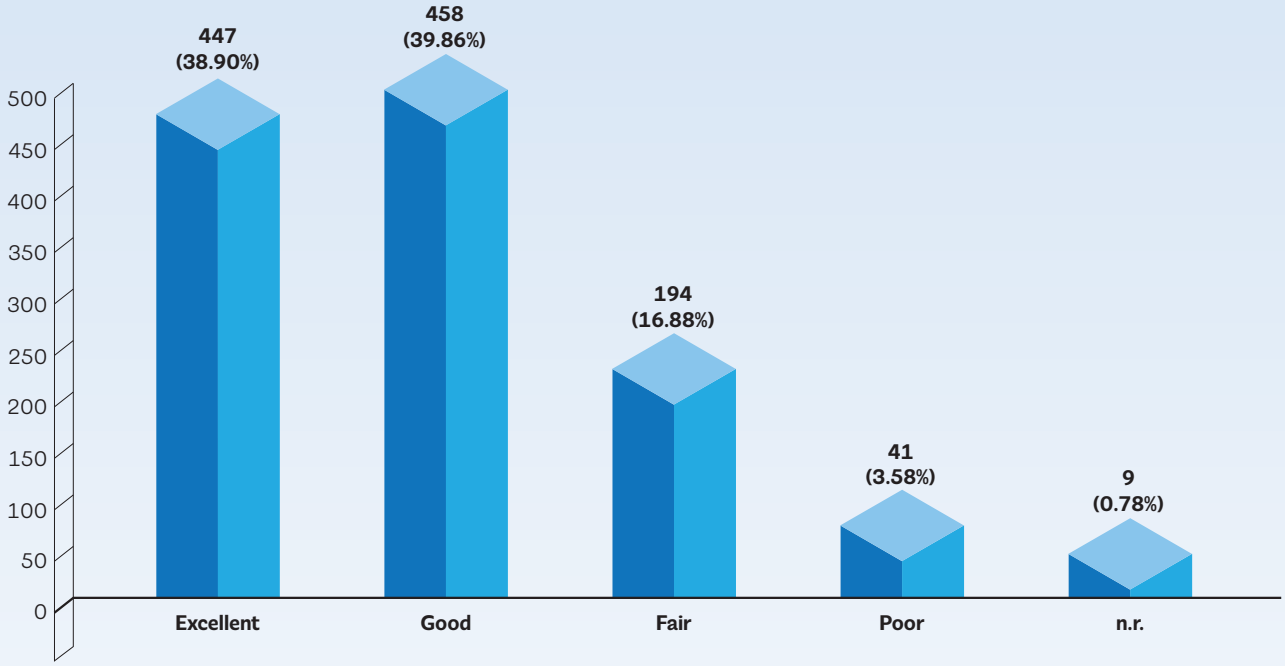
When administered together, vitamins B1, B6 and B12 accelerated the regeneration of nerve lesions.

Significant improvement in painful diabetic peripheral neuropathy symptom in 28 days[9]



* N=310.
** Neurobion tab (vitamin B1 100mg, vitamin B6 100mg, Vitamin B12 200mcg), twice a day, for 28 days.
*** 2 points improvement of neuropathy pain score versus baseline.

Parenteral administration followed by oral administration of the vitamin B combination has shown excellent efficacy in patients with polyneuropathies[9]



Global Assessment of Efficacy (Symptomatic Improvement) with vitamin B1, B6 and B12 parenteral administration followed by oral treatment (n = 1,149) n.r. = not responded.

Subjects:

Patients with polyneuropathy, neuralgia, radiculopathy and neuritis associated with pain and parasthesias (n=1,149).

Parameters:

Pain intensity, leg weakness and paresthesia – each rated as absent, mild, moderate, or severe; global assessment of efficacy and tolerability.

Treatment:

- Parenteral administration (vitamin B1 100mg, vitamin B6 100mg, vitamin B12 1.5mg).
- Followed by oral treatment (vitamin B1 100mg, vitamin B6 100mg, vitamin B12 0.25mg).
- Patients were followed for up to 4 visits, maximum 50 days.

Neurobion®
VITAMIN B1, B6, B12

Effective care for your patients with diabetic peripheral neuropathy

- Neurobion accelerates regeneration of nerve lesions in diabetic sensory polyneuropathy.[7]
- Combination of vitamin B1, B6 and B12 improves pain relief among patients with diabetic peripheral neuropathy in 28 days.[8]
- Parenteral administration followed by oral administration of vitamin B combination has shown excellent efficacy in patients with polyneuropathies.[9]

Vitamin B1 100mg
Vitamin B6 200mg
Vitamin B12 200mcg

Vitamin B1 100mg
Vitamin B6 100mg
Vitamin B12 1000mcg

* Based on IQVIA MIDAS sales from MAT12/2017 to MAT12/2018.

Abbreviated Prescribing information
Product Name: NEUROBION® COATED TABLETS and NEUROBION AMPOULE

PRESENTATION: Tablet: Each tablet contains, as active ingredients, 100mg vitamin B1 (thiamine disulfide), 200mg vitamin B6 (pyridoxine hydrochloride), 200 mcg vitamin B12 (cyanocobalamin). Injection: Each 3-mL ampoule contains, as active ingredients : Vitamin B1 (thiamine hydrochloride) 100 mg, vitamin B6 (pyridoxol hydrochloride) 100 mg, vitamin B12 1000 mcg. **INDICATIONS:** Tablet: For nerve pain expressed in one or more of the following symptoms: pricking/tingling sensation, numbness, muscle stiffness, muscle cramp, impaired sensation. Injection: For neurological and other disorders associated with disturbance of metabolic functions influenced by B complex vitamins, including diabetic polyneuropathy, alcoholic peripheral neuritis and post influenzal neuropathies. It is also recommended for the treatment of neuritis and neuralgia of the spinal nerves, especially facial paresis, cervical syndrome, low back pain, ischialgia, herpes zoster. **DOSAGE:** Tablet: 1 coated tablet three times daily, to be swallowed without chewing with a little liquid with or after meals. Injection: Neurobion is administered by intramuscular injection. In severe cases 1 ampoule daily is given until the acute symptoms subside. For follow-up therapy 2-3 ampoules are given per week. In milder conditions this dosage is sufficient from the beginning. The duration of the treatment is determined by the doctor. **CONTRAINDICATIONS:** Neurobion must not be used in patients hypersensitive to any of the active ingredients or excipients of the product. Neurobion are not suitable for the treatment of children due to the high content of active ingredients. **SPECIAL WARNINGS AND PRECAUTIONS:** Under long term treatment regular monitoring is recommended. Neurobion tablet is not recommended to be used in patients with intolerance to some sugars (i.e. rare hereditary galactose or fructose intolerance, glucose-galactose malabsorption, Lapp lactase deficiency, or sucrose-isomaltase insufficiency). **PREGNANCY AND LACTATION:** No risks have become known associated with the use of Neurobion during pregnancy at the recommended dosage. Vitamins B1, B6 and B12 are secreted into human breast milk, but risks of overdose for the infant are not known. In individual cases, high doses of vitamin B6 i.e. > 600mg daily, may inhibit the production of breast milk. **UNDESIRABLE EFFECTS:** Long term intake (>6-12 months) of daily dosage >50mg vitamin B6 may cause peripheral sensory neuropathy. Hypersensitivity reactions to vitamin B1, such as sweating, tachycardia (rapid heartbeat), and skin reactions with itching and urticaria are very rare. Gastorintestinal complaints, such as nausea, vomiting, diarrhea or abdominal pain may occur. Chromaturia ("reddish urine", appeared during the first 48 hours after an administration and typically resolves within 48 hours). In single cases, conditions of shock have been observed after treatment with vitamin B1 or B12 injections. Gastrointestinal complaints, such as nausea, vomiting, diarrhoea or abdominal pain may occur. Individual cases of acne have been reported after high parenteral dose of vitamin B12. Injection site reactions may occur. **INTERACTIONS:** The effect of L-dopa may be reduced when vitamin B6 is administered concomitantly. Pyridoxine-antogonists, e.g. isoniazid (INH), cycloserin, penicillamin, hydralazine: the efficacy of vitamin B6 may be decreased. Loop diuretics, e.g. furosemide: In long term use, the blood level of vitamin B1 may be reduced.

References:
1) Juster-Switlyk K, Gordon Smith A. F1000Res. 2016;5: pii-738. 2) Miranda-Massari JR, et al. Curr Clin Pharmacol. 2011;6: 260–273. 3) Singh R, et al. Pharmacol Res. 2014;80: 21–35. 4) Callaghan BC, et al. Lancet Neurol. 2012;11: 521–534. 5) Landmann G. Psychiatrie & Neurologie 2012;5:13-16. 6) Thomas FP. The spectrum of diabetic neuropathy. 7) Janka HU et al. The infl uence of Neurobion on temperature sensibility in patients with diabetic polyneuropathy Pharmakol Klinischeanwendung hochdosierter B-vitamine, Steinkopff verlag, Darmastadt 1991; 87-97 8) Rizvi A et al. Effi cacy of combination of vitamin B1. B6 and B12 in management of diabetic peripheral neuropathy. Pakistan Journal of medical and health sciences 2013; 7(3): 801. Available at: www.pjmhsonline.com 9) Eckart M, Schejbal P. Fortschr Med. 1992;110: 544-548. 10) Singleton CK, Martin PR. Curr Mol Med. 2001;1:197-207. 11) Beltramo E et al. Acta Diabetol. 2008;45:131-141. 12) Spinneker A et al. Nutr Hosp. 2007;22:7-24. 13) Adamo AM. Genes Nutr. 2014;9:360. 14) Kumar N. Neurologic Aspects of Cobalamin (B12) Deficiency. In: Handb Clin Neurol. 2014;120:915-926. 15) Briani C et al. Nutrients. 2013;5:4521-4539.

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