

NERVILIN-M®

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1. Product Name

NERVILIN-M® 750/1500 mg Tablet

2. Name and Strength of Active Ingredient(s)

Nervilin-M 750

Each hard gelatin capsule contains:

Pregabalin IP 75mg Methylcobalamin IP 750mcg

Nervilin-M 1500

Each hard gelatin capsule contains:

Pregabalin IP 75mg Methylcobalamin IP 1500mcg

3. Product Description

NERVILIN-M® is Combination of Pregabalin and Methylcobalamin. Pregabalin is used to relieve neuropathic pain. Methylcobalamin is a B12 containing coenzyme with an active methyl base. It plays an important role in red blood cell formation, methylation reaction, brain and nervous system functions and immune system functions.

4. Pharmacodynamics & Pharmacokinetics

Pharmacodynamics:

Pregabalin:

Pregabalin binds with high affinity to the alpha2-delta site (an auxiliary subunit of voltage-gated calcium channels) in central nervous system tissues. Although the mechanism of action of pregabalin has not been fully elucidated, results with genetically modified mice and with compounds structurally related to pregabalin (such as gabapentin) suggest that binding to the alpha2-delta subunit may be involved in pregabalin's anti-nociceptive and antiseizure effects in animals. In animal models of nerve damage, pregabalin has been shown to reduce calcium-dependent release of pro-nociceptive neurotransmitters in the spinal cord, possibly by disrupting alpha2-delta containing-calcium channel trafficking and/or reducing calcium currents.

Methylcobalamin:

(1) Methylcobalamin is a kind of endogenous coenzyme B12 :

As a coenzyme of methionine synthetase, methylcobalamin plays an important role in transmethylation in the synthesis of methionine from homocysteine.

(2) Methylcobalamin is well transported to nerve cell organelles, and promotes nucleic acid and protein synthesis :

Experiments in rats show that methylcobalamin is better transported to nerve cell organelles than cyanocobalamin and promotes nucleic acid and protein synthesis more than cobalamide does. Experiments with cells from the brain origin and spinal nerve cells in rats also show methylcobalamin to be involved in the synthesis of thymidine from deoxyuridine, promotion of deposited folic acid utilization and metabolism of nucleic acid.

(3) Methylcobalamin promotes axonal transport and axonal regeneration :

In rat models with streptozotocin-induced diabetes mellitus, methylcobalamin normalizes axonal skeletal protein transport in sciatic nerve cells. Methylcobalamin exhibits neuropathologically and electrophysiologically inhibitory effects on nerve degeneration in neuropathies induced by drugs, such as adriamycin, acrylamide, and vincristine (in rats and rabbits), models of axonal degeneration in mice and neuropathies in rats with spontaneous diabetes mellitus.

(4) Methylcobalamin promotes myelination (phospholipid synthesis) :

Methylcobalamin promotes the synthesis of lecithin which is the main

constituent of medullary sheath lipid. It also increases myelination of neurons in rat tissue culture more than cobalamide does.

(5) Methylcobalamin restores delayed synaptic transmission and diminished neurotransmitters back to normal :

Methylcobalamin restores end-plate potential induction early by increasing nerve fiber excitability in the crushed sciatic nerve in rats. In addition, methylcobalamin normalizes diminished levels of acetylcholine in brain tissue of rats fed with a choline-deficient diet.

Pharmacokinetics:

Pregabalin:

Absorption and Distribution:

Following oral administration of Pregabalin capsules under fasting conditions, peak plasma concentrations occur within 1.5 hours. Pregabalin oral bioavailability is ≥90% and is independent of dose. Following single- (25 to 300 mg) and multiple- dose (75 to 900 mg/day) administration, maximum plasma concentrations (C_{max}) and area under the plasma concentration-time curve (AUC) values increase linearly. Following repeated administration, steady state is achieved within 24 to 48 hours. Multiple-dose pharmacokinetics can be predicted from single-dose data. The rate of pregabalin absorption is decreased when given with food, resulting in a decrease in C_{max} of approximately 25% to 30% and an increase in T_{max} to approximately 3 hours. However, administration of pregabalin with food has no clinically relevant effect on the total absorption of pregabalin. Therefore, pregabalin can be taken with or without food.

Metabolism and Elimination:

Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabeled pregabalin, approximately 90% of the administered dose was recovered in the urine as unchanged pregabalin. The N-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0.9% of the dose.

Methylcobalamin:

(1) Absorption:

Vitamin B12 substances bind to intrinsic factor, a glycoprotein secreted by the gastric mucosa, and are then actively absorbed from the gastrointestinal tract. Absorption is impaired in patients with an absence of intrinsic factor, with a malabsorption syndrome or with disease or abnormality of the gut, or after gastrectomy. Absorption from the gastrointestinal tract can also occur by passive diffusion; little of the vitamin present in food is absorbed in this manner although the process becomes increasingly important with larger amounts such as those used therapeutically.

(2) Distribution:

Vitamin B12 is extensively bound to specific plasma proteins called transcobalamins; transcobalamin II appears to be involved in the rapid transport of the cobalamins to tissues. Vitamin B12 is stored in the liver. Vitamin B12 diffuses across the placenta and also appears in breast milk.

(3) Excretion:

Vitamin B12 is excreted in the bile, and undergoes extensive enterohepatic recycling; part of a dose is excreted in the urine, most of it in the first 8 hours; urinary excretion, however, accounts for only a small fraction in the reduction of total body stores acquired by dietary means.

5. Indications:

Pregabalin:

Management of neuropathic pain associated with diabetic peripheral neuropathy

Management of postherpetic neuralgia
Adjunctive therapy for the treatment of partial-onset seizures in patients 1 month of age and older
Management of fibromyalgia
Management of neuropathic pain associated with spinal cord injury

Methylcobalamin:
Peripheral neuropathies

6. Recommended Dose and Administration

Pregabalin:

INDICATION	DOSING REGIMEN	MAXIMUM DOSE
DPN Pain	3 divided doses per day	300 mg/day within 1 week
PHN	2 or 3 divided doses per day	300 mg/day within 1 week. Maximum dose of 600 mg/day
Adjunctive Therapy for Partial Onset Seizures in Patients 4 Years of Age and Older	2 or 3 divided doses per day	Maximum dose of 600 mg/day.
Fibromyalgia	2 divided doses per day	300 mg/day within 1 week. Maximum dose of 450 mg/day.
Neuropathic Pain Associated with Spinal Cord Injury	2 divided doses per day	300 mg/day within 1 week. Maximum dose of 600 mg/day.

Methylcobalamin:
Peripheral neuropathies Tablets:
The usual adult dosage for oral use is 3 tablets (1500mcg) daily in three divided doses.

7. Contraindication

Pregabalin:
Contraindicated in patients with known hypersensitivity to pregabalin or any of its components. Angioedema and hypersensitivity reactions have occurred in patients receiving pregabalin therapy

Methylcobalamin:
Contraindicated in patients who are hypersensitive to this drug or any component of this product or other B12 containing products.

8. Special Populations:

Geriatrics:
Pregabalin oral clearance tended to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with age-related decreases in CL_{cr}. Reduction of pregabalin dose may be required in patients who have age-related compromised renal function

Pregnancy and Lactation:

Pregabalin:
This drug should only be given during pregnancy when there are no alternatives and benefit outweighs risk

Methylcobalamin:
Not recommended in pregnant and lactating women.

9. Storage Condition

Store Nervilin-M® at room temperature, away from light & moisture.
• Keep all medications away from children and pets.
• Do not flush medications down the toilet or pour them into a drain unless instructed to do so.
• Properly discard this product when it is expired or no longer needed.

10. Dosage Forms and packaging available

Nervilin-M 750
Each box contains 10x10 capsule in a blister pack.
Nervilin-M 1500
Each box contains 10x10 capsule in a blister pack.