*For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only*

**PRODUCT SAFETY GUIDELINES**

**READ PACKAGE INSERT CAREFULLY BEFORE USE**

# NEUROBION FORTE RF
# Injection of Mecobalamin, Pyridoxine Hydrochloride & Nicotinamide

## QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2 ml ampoule contains:

| | |
|---|---|
| Mecobalamin IP | 1000 mcg. |
| Pyridoxine Hydrochloride IP | 100 mg. |
| Nicotinamide IP | 100 mg. |
| Benzyl Alcohol IP (as preservative) | 2 % w/v |
| Water for Injections IP | q.s. |

Appropriate overages of vitamins are added to compensate loss during storage

## PHARMACEUTICAL FORM

Solution for injection
Clear and dark red colour solution

## DESCRIPTION

Mecobalamin is Coα-[α-5,6-Dimethyl-1*H*-benzoimidazolyl)]-Coβ-methylcobamide. The molecular formula of mecobalamin is $C_{63}H_{91}CoN_{13}O_{14}P$ and the molecular weight is 1344.38.

Pyridoxine is 5-hydroxy-6-methylpyridine-3,4-dimethanol hydrochloride. The molecular formula of Pyridoxine Hydrochloride is $C_8H_{11}NO_3$, HCl and the molecular weight is 205.6.

Nicotinamide is pyridine-3-carboxamide. The molecular formula of Nicotinamide is $C_6H_6N_2O$ and the molecular weight is 122.1.

## PHARMACOLOGICAL PROPERTIES

**Pharmacodynamic properties**
**Pharmacotherapeutic Group**
Mecobalamin, Pyridoxine HCl, Nicotinamide

**ATC code:**
Mecobalamin- B03BA054; Pyridoxine- A11HA024; Nicotinamide – A11HA01

**Mechanism of Action:**
Peripheral neuropathy has a variety of systemic, metabolic, and toxic causes. The most common treatable causes include diabetes mellitus, hypothyroidism, and nutritional deficiencies. Treatment should address the underlying disease process, correct any nutritional deficiencies, and provide

symptomatic treatment.

Cobalamin is an essential cofactor for methyl tetrahydrofolate methyltransferase in the trans methylation process whereby homocysteine is converted to methionine which is associated with the biosynthesis of myelin protein DNA in peripheral nerves. It is also concerned with the biosynthesis of lecithin, which is indispensable to myelination and nerve regeneration, hence it has an effect on nerve repair in diabetic neuropathy[6]. Moreover, preclinical studies have demonstrated that a high dose of Mecobalamin promotes neurite outgrowth and neuronal survival, and its continuous administration enhances nerve regeneration in a rat sciatic nerve injury model. Similarly, Watanabe et al. reported that an ultra-high dose Mecobalamin therapy promotes nerve regeneration in an experimental model of acrylamide neuropathy. Studies also have demonstrated potential analgesic effects of mecobalamin on neuropathic pain.

Vitamin $B_6$, traditionally referred to as Pyridoxine, covers a group of compounds that are metabolically interchangeable. Pyridoxine is an essential cofactor in various transamination, decarboxylation, glycogen hydrolysis, and synthesis pathways involving carbohydrate, sphingolipid, amino acid, heame, and neurotransmitter metabolism. Pyridoxine deficiency causes blood, skin, and nerve changes. This vitamin is unique in that either deficiency or excess can cause peripheral neuropathy.

Nicotinamide is the water-soluble amide form of vitamin B3, is a key component of the metabolic pathway involved in the production of nicotinamide adenine dinucleotide (NAD+).The enzyme, nicotinamide phosphoribosyl transferase (NAMPT), catalyzes the synthesis of nicotinamide mononucleotide (NMN) from nicotinamide. Its role in the metabolic pathway for the biosynthesis of NAD (oxidized form NAD+; reduced form NADH) suggests its importance in cells that are sensitive to decreases in NAD levels, such as neurons. NAD homeostasis has also been found to be altered with ageing. Thus, by influencing levels of NAD+ within neurons, nicotinamide may play a key role in neuronal maturation and neuroprotection.

**Pharmacokinetic properties**

Mecobalamin is extensively bound to specific plasma proteins called transcobalamins; transcobalamin II appears to be involved in the rapid transport of the cobalamins to tissues. $B_{12}$ diffuses across the placenta and appears in breast milk of nursing mothers. The liver is the predominant storage site for mecobalamin. Mecobalamin is excreted in bile and reabsorbed via the enterohepatic circulation wherein part of a dose is excreted in the urine, most of it in the first 8 hours.

Pyridoxine and its other derivatives –undergo biotransformation in liver into the active coenzyme pyridoxal 5'- phosphate (P5P), which is then exported from the liver bound to albumin. Uptake into tissue is by extracellular de-phosphorylation, followed by metabolic trapping intracellularly as P5P. The metabolite 4-pyridoxic acid and other inactive metabolites are excreted in the urine. As the dose increases, proportionally greater amounts are excreted unchanged in the urine. Pyridoxal crosses the placenta and is distributed into breast milk. Elimination half-life of pyridoxine is 15-20 days.

Nicotinamide is readily absorbed parenterally and from all parts of the gastrointestinal tract and peak concentrations are achieved in humans within about 1 hour of oral ingestion of standard preparations. Nicotinamide can be oxidized to nicotinamide-N- oxide, methylated to N-methyl-nicotinamide or hydroxylated to 6-hydroxynicotinamide. There is no evidence that nicotinamide is metabolized to nicotinic acid in rodents or humans. Nicotinamide disappears rapidly from the circulation and is distributed in all tissues. It has a high hepatic extraction ratio and plasma clearance can be reduced in

patients with hepatic insufficiency. Hepatic methylation as a methyl donor is important in the detoxification of nicotinamide. The product of this reaction N-methyl-nicotinamide is excreted by the kidneys whereas nicotinamide is reabsorbed by the renal tubes. For this reason, only small amounts of the unchanged nicotinamide appear in the urine even at pharmacological doses of nicotinamide. N-methyl-nicotinamide is oxidized in the liver, a process that is saturated at high circulating concentrations, and the end products are N- methyl-2-pyridone-5-carboxylic acid amide and N-methyl-4-pyridone-3-carboxylic acid amide.

**Preclinical Safety Data**

**Toxicity**

***Mecobalamin*:** There is limited data on the oral toxicity of mecobalamin in laboratory animals. The reported acute oral toxicity ($LD_{50}$) in rats were >5gm/kg (5000mg/kg).

A review of pyridoxine toxicity studies in animal suggests that both acute and chronic toxicities are relatively low. In acute toxicity study, $LD_{50}$ in rat is 4000 mg/kg and in mouse is 5500 mg/kg. The oral administration of 150–200 mg of pyridoxine/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 pyridoxine.

The $LD_{50}$ of nicotinamide in rats is 1.68 g/kg when given subcutaneously. The $LD_{50}$ in mice is estimated as 4.5 g/kg when given orally and 2.5 g/kg when given intravenously. The therapeutic index of the preparation is correspondingly wide.

**Carcinogenicity and genotoxicity**

***Mecobalamin*:** There is no evidence suggesting that mecobalamin is carcinogenic or genotoxic *in vitro* or *in vivo* in humans.

***Pyridoxine***: Mutagenic effects of pyridoxine are not to be expected under the conditions of clinical use. There are no long-term animal studies available on the tumorigenic potential of pyridoxine.

Pyridoxine 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 pyridoxine induced damage to spermatogenesis.

A study demonstrated that no apparent carcinogenic action occurred when nicotinamide was administered separately as 1% solutions (the dose high enough to produce carcinogenic effect) in drinking water for life to Swiss mice from 6 weeks of age.

Data on genotoxicity have not been identified.

**Pregnancy & Lactation**

There are only insufficient animal studies on the effect of similar combination medicinal product on pregnancy, embryo-fetal, prenatal, and postnatal development.

Mecobalamin: Mecobalamin crosses the placenta during pregnancy and is excreted in the breast milk.

Pyridoxine: There are only insufficient animal studies on the effect of pyridoxine on pregnancy, embryo-fetal, prenatal, and postnatal development. High concentrations of pyridoxine can inhibit the

production of breast milk. Data on the extent of secretion into breast milk from animal studies are not available.

The teratogenic effects of nicotinamide have been studied in chick embryos by injection of the vitamin into the yolk sack of the egg in doses of 2-19 mg/egg. These experiments provide no evidence that nicotinamide is teratogenic by itself.

Nicotinamide is transferred actively across placenta and into breast milk.

## CLINICAL PARTICULARS

### Therapeutic indications

NEUROBION FORTE® RF is indicated in following conditions

- Peripheral Neuropathy
- Clinical conditions resulting in $B_6$, $B_{12}$, niacin deficiencies
    - When oral therapy is not feasible in critically ill patients, ICU patients, excessive vomiting cases
    - In noncompliant patients to ensure compliance

### Posology and method of administration

In severe (acute) cases: One ampoule daily until the acute symptoms subside (based on clinician's judgement on clinical condition).

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

Neurobion Forte RF injection can be administered either by slow intravenous injection after dilution or deep intramuscularly once daily (or as directed by the physician) depending on the nature and severity of peripheral neuropathy or states resulting in $B_6$, $B_{12}$, and Niacin deficiencies.

### Contraindications

Contraindicated in patients with known hypersensitivity to either of the ingredients

### Special warnings and precautions for use

Neurobion Forte RF Injection is meant for One Time Use only. The ampoule should not be stored for repeat use and should be discarded after single use.

For use in adult.

**Mecobalamin:** Due to presence of Mecobalamin, short-term parenteral administration of this medication may temporarily impair the diagnosis of funicular myelosis or pernicious anemia**.** Mecobalamin should be used cautiously in patients with hypertension, cardiovascular and lung disease. Use of Mecobalamin is not recommended in children younger than 12 years of age as safety and effectiveness in this age group have not been confirmed. Mecobalamin should be cautiously used in

patients with hematological concerns, as, according to case report data, vitamin $B_{12}$ and its analogues may lead to polycythemia vera in such patients.

Mecobalamin should be used cautiously in patients with subnormal levels of potassium, as it may result in fatal hypokalemia in susceptible individuals.

Long-term use of large doses of pyridoxine is associated with the development of severe peripheral neuropathies (Please refer to section "**Undesirable effects**"). If symptoms of peripheral sensory neuropathy (paresthesia) occur, the dosage should be reviewed and treatment with the medicinal product discontinued, if necessary.

Large doses of nicotinamide should be administered with caution in patients with a history of jaundice, liver disease, or diabetes mellitus.

**Interaction with other medicinal products and other forms of interaction**

**Mecobalamin:**
Long term treatment with metformin in patients with Type 2 diabetes receiving insulin increases the risk of vitamin $B_{12}$ deficiency, which results in higher levels of homocysteine. Moreover, the negative effect of metformin on vitamin $B_{12}$ concentrations increases over time. Hence routine assessment of vitamin $B_{12}$ levels should be conducted during long term treatment with metformin.

Absorption of vitamin $B_{12}$ from the gastrointestinal tract may be reduced by neomycin, amino alicyclic acid, anticonvulsants, nitrous oxide, potassium chloride, histamine $H_2$-antagonists, omeprazole, colchicine, and excessive alcohol consumption.

Serum concentrations may be decreased by use of oral contraceptives.

Parenteral chloramphenicol may attenuate the effect of vitamin $B_{12}$ in anemia.

Pyridoxine reduces the effects of levodopa, but this does not occur if a dopa decarboxylase inhibitor is also given.

Pyridoxine reduces the activity of altretamine.

Decrease serum concentrations of phenobarbital and phenytoin have been reported with concomitant use of Mecobalamin.

Drugs like hydralazine, isoniazid, penicillamine, and oral contraceptives may increase the requirements for pyridoxine.

Concomitant use of niacinamide and antiepileptic drugs, specifically carbamazepine, diazepam, and sodium valproate, apparently potentiates the anticonvulsant action of

these drugs. In addition, niacinamide may decrease clearance of carbamazepine when used simultaneously.

**Pregnancy and Lactation**

There is no evidence relating to mecobalamin and teratogenicity or adverse effects on fertility or post-

natal development. Mecobalamin crosses the placenta during pregnancy and is excreted in the breast milk

Data on exposed pregnancies indicate no adverse effects of pyridoxine in therapeutic doses on pregnancy or the health of the fetus or newborn child, or during lactation. Animal studies are insufficient with respect to effects on pregnancy, embryonal/fetal development, parturition, or postnatal development.

Large doses of nicotinamide should be avoided in pregnancy Therefore Caution should be exercised when prescribing NEUROBION FORTE® RF Injection to pregnant women.

Caution should be exercised when using NEUROBION FORTE® RF Injection in nursing mothers.

**Effects on ability to drive and use machines**

There is no data to derive any conclusion on the effects of NEUROBION FORTE® RF Injection on the ability to drive and use heavy machines.

**Undesirable effects**

***Mecobalamin*:** In most cases, mecobalamin is nontoxic, even in large doses. The side effects reported with use of oral mecobalamin were mild diarrhea, bloated feeling, dyspnea, headache, *polycythemia vera*, hypokalemia, itching, nausea, vomiting transitory exanthema, allergic reaction (rash, swelling of the mouth, face, lips or tongue)

Long-term intake (> 6-12 months) of a daily dosage > 50 mg Pyridoxine may cause peripheral sensory neuropathy [20] In addition to this Paresthesia, somnolence, and low serum folic acid levels have been reported with the use of Pyridoxine Hydrochloride Injection

At recommended doses, Nicotinamide is expected to be well tolerated. The side effects reported with use of Nicotinamide are Dizziness, headache, hyperglycemia, nausea, vomiting, diarrhea, elevations in liver function tests, hepatotoxicity, blurred vision, flushing, rash.

**Overdose**

Over dosage with Mecobalamin has not been reported. There have been various scientific studies where test subjects were given extremely high doses of Mecobalamin (often several thousand times the Vitamin $B_{12}$ RDA) for extended periods of time (months or years). None of this research suggested that these large quantities posed any toxicity threat, although allergic reactions, eczematous skin alterations and a benign form of acne have been observed after high-dose parenteral administration[20]. This may largely be due to the fact that Mecobalamin is a water soluble, and any excess will be excreted through urine The toxic potential of Pyridoxine can be considered as very low. Long-term treatment (> 6-12 months) of a daily dosage > 50 mg vitamin Pyridoxine may, however, cause peripheral sensory neuropathy. Continuous intake of Pyridoxine 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 anemia and seborrheic dermatitis have been described after administration of more than 2 g daily.

Overdose with nicotinamide does not appear to have been reported. Adverse effects of the related nicotinic acid are usually not serious and subside on withdrawal of the drug Supportive measures

should be undertaken in the event of an overdose.

## CLINICAL STUDIES

S Jayaram et. Al. 2009, Peripheral neuropathy (PN) is characterized by pain, numbness and tingling in the extremities and slow nerve conduction. It affects a significant percentage of the Indian population and can be extremely debilitating. Around 7% of patients usually have neuropathy upon diagnosis of diabetes, and the incidence approaches 50% for patients with diabetes for more than 25 years.
Diabetes is the most common etiological factor for peripheral neuropathy (PN). While conventional theory says that prolonged hyperglycemia results in the complications associated with diabetes, including neuropathy, a recent study found that PN can manifest even in individuals with abnormal glucose tolerance, a prediabetes condition. A combination of methylcobalamin, pyridoxine and nicotinamide thus has synergistic effect on the damaged nerves in diabetic neuropathy which protects the nerves from further damage, restores its structural and functional integrity and causes a recovery of function. Azhary H et al.2010, Peripheral neuropathy has a variety of systemic, metabolic, and toxic causes. The most common treatable causes include diabetes mellitus, hypothyroidism, and nutritional deficiencies. The diagnosis requires careful clinical assessment, judicious laboratory testing, and electro diagnostic studies or nerve biopsy if the diagnosis remains unclear. A systematic approach begins with localization of the lesion to the peripheral nerves, identification of the underlying etiology, and exclusion of

potentially treatable causes. Treatment should address the underlying disease process, correct any nutritional deficiencies, and provide symptomatic treatment.

Kathleen A. 2006 Alternative therapies, on the other hand, are typically without side effects and address nutrient deficiencies, oxidative stress, and other etiological factors associated with the development of PN. Alpha-lipoic acid, acetyl-L-carnitine, benfotiamine, methyl cobalamin, and topical capsaicin are among the most well- researched alternative options for the treatment of PN. A questionnaire-based study examined the use of alternative treatments for PN in 180 consecutive outpatients at St. Elizabeth's Medical Center in Boston, MA. Seventy-seven patients (43%) reported using alternative therapies; 37 of 77 (48%) employed more than one type of alternative treatment.
Hammond N et al. 2013, Malnutrition can affect all areas of the nervous system. A unique class of peripheral neuropathy with coexistent myelopathy, also called myeloneuropathy, can also been seen with nutritional neuropathies. Myeloneuropathy has been described with deficiencies of vitamin B12 and copper.

The neuropathy associated with B12 deficiency usually begins with sensory symptoms in the feet. Early diagnosis is critical since patients with advanced disease may be left with major residual disability. Common treatment regimen includes administration of 1000 mcg intramuscularly daily for 5–7 days, followed by 1000 mcg IM monthly. Other approaches are a once-a-week injections for four weeks, and then monthly injections. Either is probably acceptable. B12 levels should be monitored occasionally to prevent inadequate treatment or non-compliance. Vitamin B6, or pyridoxine, is unique in that either a deficiency or an excess can cause a neuropathy. Vitamin B6, or pyridoxine, is unique in that either a deficiency or an excess can cause a neuropathy.

Vitamin B6 toxicity produces a sensory ataxia, areflexia, and impaired cutaneous sensation. Patients often complain of burning or paresthesia's. Electro diagnostic testing usually shows a sensory neuronopathy, but with severe toxicity motor nerves can be affected as well. Symptoms of toxicity can be seen with doses as low as 100 mg per day. Ang CD et al. 2008, reviewed of 13 trials on diabetic and alcoholic peripheral neuropathy with a total of 741 participants showed Vitamin B complex when

given in a higher dose administered for four weeks was more efficacious than a lower dose in reducing pain and other clinical problems based on another study. Two to eight weeks of treatment with vitamin B was less efficacious than alpha-lipoic acid, cilostazol or cytidine triphosphate in short-term improvement of clinical and nerve test findings. All these findings require confirmation in larger studies before they can be accepted as definite. Vitamin B is generally well-tolerated with only a few reports of mild side effects.

## PHARMACEUTICAL PARTICULARS

### Shelf life

Please refer carton or label.

### Dosage

As directed by Physician

### Special precautions for Storage, Handling & Disposal

Store at or below 30ºC. Protect from light

### Nature and contents of container

Pack of 2ml Ampoules.

### Date of revision

27/06/2023

### Manufactured by

For manufacturing site details refer pack

**Marketed by:**
Procter & Gamble Health Limited
P&G Plaza, Cardinal Gracias Road,
Chakala, Andheri E, Mumbai 400099.