

PRODUCT MONOGRAPH

MYELOGEN FORTE NU

(Methylcobalamin 1500 mcg + Benfotiamine 100 mg + Alpha Lipoic Acid 100 mg +
Folic acid 1.5 mg + Pyridoxine Hydrochloride 3mg)

For Diabetic Peripheral Neuropathy

Manufactured By:

Panacea Biotec Limited.

(Address as on Package)

Date of Preparation:

(04 June 2019)

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For Diabetic Peripheral Neuropathy

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Approved Indications
Oral	One Capsule of MYELOGEN FORTE NU contains Methylcobalamin 1500 mcg + Benfotiamine 100 mg + Alpha Lipoic Acid 100 mg + Folic acid 1.5 mg + Pyridoxine Hydrochloride 3mg	Diabetic Peripheral Neuropathy in Adults.

INDICATIONS AND CLINICAL USE

Diabetic Peripheral Neuropathy in adults developed as a late manifestation of uncontrolled or long-standing diabetes that are treated with more than one antidiabetic drugs and significantly affects quality of life.

CONTRAINDICATIONS Hypersensitivity to any of the components of formulation.

WARNINGS AND PRECAUTIONS

Methylcobalamin:

Vitamin B12 should, if possible, not be given to patients with suspected vitamin B12 deficiency without first confirming the diagnosis. Where it is desirable to start therapy immediately, combined treatment for both deficiencies may be started once suitable samples have been taken to permit diagnosis of the deficiency, and the patient converted to the appropriate treatment once the cause of the anaemia is known. Regular monitoring of the blood is advisable. Although the haematological symptoms of B12 deficiency and folate deficiency are similar, it is important to distinguish between them since the use of folate alone in B12-deficient megaloblastic anaemia can improve haematological symptoms without preventing aggravation of accompanying neurological symptoms, and may lead to severe nervous system sequelae such as subacute combined degeneration of the spinal cord. Conversely, folate may mask vitamin B12 deficiency.

Benfotiamine:

Do not exceed the stated dose. Keep out of the reach of children. Any individual who has a specific health problem or is taking medications must first seek advice from his or her personal physician or healthcare provider before starting Benfotiamine.

Alpha Lipoic Acid:

Apha-lipoic acid can interact with antidiabetic drugs, to further reduce blood sugar levels, resulting in hypoglycaemia. Can reduce the levels of levothyroxine.

Usage in pregnancy

Methylcobalamin:

Contraindicated.

There are no data available for Mecobalamin to be used in pregnant women.

Pediatric use

Safety and effectiveness in children have not been established.

Lactation

There are no data available for mecobalamin to be used in lactating women. However, since vitamin B12 is distributed into breast milk, The American Academy of Pediatrics considers its use to be usually compatible with breast feeding.

Consult your personal physician or healthcare provider before starting Myelogen Forte NU.

ADVERSE REACTIONS

Side Effects:

Mecobalamin (Methylcobalamin)

Gastrointestinal

Anorexia, nausea, vomiting and diarrhoea were observed with a frequency of <5%.

Anaphylactoid Reaction

Anaphylactoid reaction such as decrease in blood pressure or dyspnoea may occur with mecobalamin. Patients should be carefully observed. In the event of such symptoms, treatment should be discontinued immediately and appropriate measures taken.

Benfotiamine

Burning sensation, Tightness sensation, Headache, Nausea, Sleepiness, Stomach upset, Pricking sensation, Tingling sensation.

DRUG INTERACTIONS

Absorption of vitamin B12 from the gastrointestinal tract may be reduced by neomycin, aminosalicylic acid, histamine H2-antagonists, omeprazole, and colchicine.

Serum concentrations may be decreased by use of oral contraceptives.

Many of these interactions are unlikely to be of clinical significance but should be taken into account when performing assays for blood concentrations.

Renal impairment: Data is not available.

Hepatic impairment: Data is not available.

Pregnancy: Contraindicated

Lactation: Contraindicated

Pediatric use: Data is not available.

Geriatric use: Data is not available.

Drug Abuse and Dependence: Data is not available.

DOSAGE AND ADMINISTRATION

Myelogen Forte NU is given as 1 Capsule per day.

Method of administration

Myelogen Forte NU should be taken orally may be with or without food.

Overdosage:

Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans

Methylcobalamin has extremely low toxicity and even taking it in enormous doses appears not to be harmful to healthy individuals.. Peripheral vascular thrombosis has been reported.

There can be hypoglycemia in case of overdosage of alpha lipoic acid.

ACTION AND CLINICAL PHARMACOLOGY

Pharmacodynamics

Mecobalamin (Methylcobalamin)

Methylcobalamin is one of two active endogenous coenzymes used by B-12 dependent enzymes in the body, and is specifically the B-12 form used by 5-methyltetrahydrofolate-homocysteine methyl transferase (MTR), also known as methionine synthase. Mecobalamin plays an important role in transmethylation as a coenzyme of methionine synthetase in the synthesis of methionine from homocysteine. It also enhances the formation of lecithin (another major component of the myelin sheath).

Methylcobalamin is notable for being one of the few examples in nature of a bona fide organometallic bond.

Mecobalamin is well transported to nerve cell organelles, and promotes nucleic acid and protein synthesis. Mecobalamin is better transported to nerve cell organelles than cyanocobalamin in rats. It has been shown in experiments with cells from the brain origin and spinal nerve cells in rats to be involved in the synthesis of thymidine from deoxyuridine, promotion of deposited folic acid utilization and metabolism of nucleic acid. Also, Mecobalamin promotes nucleic acid and protein synthesis in rats more than cobamamide does.

Mecobalamin promotes axonal transport and axonal regeneration. Mecobalamin normalizes axonal skeletal protein transport in sciatic nerve cells from rat models with streptozotocin-induced diabetes mellitus. It 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.

Mecobalamin promotes myelination (phospholipid synthesis). Mecobalamin promotes the synthesis of lecithin, the main constituent of medullary sheath lipid and increases myelination of neurons in rat tissue culture more than cobamamide does.

Mecobalamin restores delayed synaptic transmission and diminished neurotransmitters to normal. Mecobalamin restores end-plate potential induction early by increasing nerve fiber

excitability in the crushed sciatic nerve in rats. In addition, Mecobalamin normalizes diminished brain tissue levels of acetylcholine in rats fed a choline-deficient diet.

Benfotiamine

Thiamine-derived compounds were discovered from the plants of *Allium* genus such as onions, shallots and leeks and named as allithiamines. The most effective compound of allithiamine family having the anti-AGEs property was subsequently identified and named as benfotiamine. The benfotiamine is a lipid-soluble congener of thiamine having a unique open thiazole-ringed structure that enables it to enter directly through the cell membrane resulting in enhanced bioavailability.

Benfotiamine corrects thiamine deficiency and decreases the incidence of neuropathies, prevents increase in UDP-N-acetyl glucosamine (UDP-GlcNAc) and prevents the formation of advanced glycation end products (AGE) in diabetic neuropathy, increases transketolase activity and prevents hyperglycemic damage, corrects imbalances in the polyol pathway thereby protecting endothelial cells from glucose-induced damage, normalizes cell replication rate and prevents apoptosis and protein kinase C (PKC) activity and prevents nuclear factor-kappa B (NF- κ B) activation in the retina of diabetics.

Chemically benfotiamine is S-[(Z)-2-[(4-amino-2-methylpyrimidin-5-yl)methylformylamino]-5-phosphonoxy-pent-2-en-3-yl] benzenecarbothioate. Unlike thiamine, the chemical structure of benfotiamine has an open thiazole ring, which closes once the compound is absorbed, producing biologically active thiamine.

Oral administration of benfotiamine leads to significant increases in thiamine, thiamine monophosphate and thiamine diphosphate levels in blood and liver but not in the brain. This difference is with the known pharmacological profile of benfotiamine, i.e., the beneficial effects of the drug concern with peripheral tissues but not the central nervous system. Due to its fine pharmacological profile, benfotiamine may be preferred in the treatment of relevant indications.

Alpha Lipoic Acid

Folic Acid

Folic acid is a B complex vitamin containing a pteridine moiety linked by a methylene bridge to para-aminobenzoic acid, which is joined by a peptide linkage to glutamic acid. Folic acid acts as cofactor for transformylation reactions in biosynthesis of purines and thymidylates of nucleic acids. Folic acid is required for normal nerve growth. Myelin consists of lecithin and ethanolamine. S-Adenosyl Methionine provides the methyl groups for conversion of ethanolamine to lecithin. If there is Folate deficiency, there is increased ethanolamine and less amounts of lecithin which is more important for myelin regeneration. Interference with the methylation reaction may lead to neuropathy. Folic acid deficiency may also cause axonal degeneration.

Pyridoxine Hydrochloride

The chemical name of Vitamin B6 is 2-methyl-3-hydroxy-4, 5-bis (hydroxymethyl) pyridine hydrochloride. Natural substances that have vitamin B6 activity are pyridoxine in plants and pyridoxal or pyridoxamine in animals. All these forms of vitamin B6 are converted to pyridoxal phosphate by the enzyme pyridoxal kinase. The physiologically active forms of

vitamin B6 are pyridoxal phosphate (codecarboxylase) and pyridoxamine phosphate. Riboflavin is required for the conversion of pyridoxine phosphate to pyridoxal phosphate.

Vitamin B6 acts as a coenzyme in the metabolism of protein, carbohydrate, and fat. In protein metabolism, it participates in the decarboxylation of amino acids, conversion of tryptophan to niacin or to serotonin (5-hydroxytryptamine), deamination, and transamination and transulfuration of amino acids. In carbohydrate metabolism, it is responsible for the breakdown of glycogen to glucose-1-phosphate.

Pharmacokinetics

Mecobalamin (Methylcobalamin)

Evidence indicates mecobalamin is utilized more efficiently than cyanocobalamin to increase levels of one of the coenzyme forms of vitamin B12. The quantity of cobalamin detected following a small oral dose of mecobalamin is similar to the amount following administration of cyanocobalamin; but significantly more cobalamin accumulates in liver tissue following administration of mecobalamin. Human urinary excretion of mecobalamin is about one-third that of a similar dose of cyanocobalamin, indicating substantially greater tissue retention. Peak plasma concentrations occur three hours after oral administration. It is mainly excreted through the kidney.

Folic Acid

Folic acid is rapidly absorbed mainly from the duodenum and jejunum. Its peak plasma concentration is achieved within 0.5 to 1 hour. It is extensively bound to plasma protein. Principal site of storage is the liver. It is also concentrated in the CSF and enters the breast milk. Folic acid undergoes conversion in the plasma and liver to the metabolically active 5-methyltetrahydrofolate. The unchanged drug and metabolites are excreted through the urine.

Pyridoxine Hydrochloride

The amount of pyridoxine in the body varies from 16 to 25 mg. Its half-life ranges from 15 to 20 days. Vitamin B6 is degraded to 4-pyridoxic acid in the liver. This metabolite is excreted mainly in the urine.

STORAGE AND STABILITY

Keep out of reach or sight of children and pets.
Myelogen Forte NU should be stored in a cool, dry and dark place.
Protect from light.

SPECIAL HANDLING INSTRUCTIONS

No special requirements.

DOSAGE FORMS: Capsules for Oral Administration

COMPOSITION:

MYELOGEN FORTE NU:

Methylcobalamin	1500 mcg
Benfotiamine	100 mg
Alpha Lipoic Acid	100 mg
Folic Acid	1.5 mg
Pyridoxine Hydrochloride	3 mg

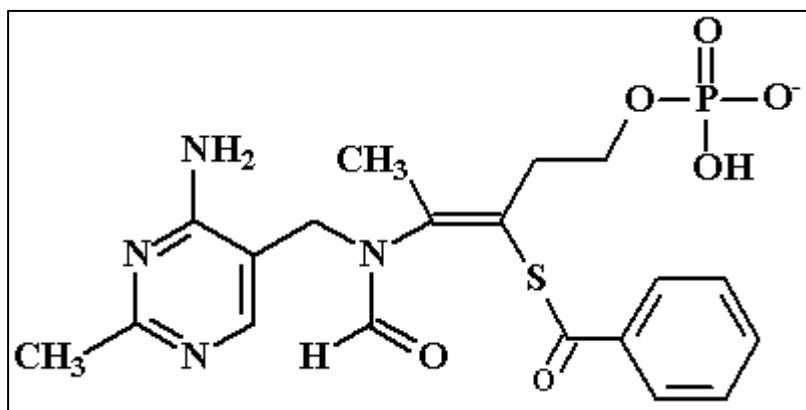
PACKAGING:

MYELOGEN FORTE NU: 10 Capsules per strip

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Benfotiamine
Chemical name:	S-[2-[(4-amino-2-methylpyrimidin-5-yl)methyl-formylamino]-5-phosphonooxypent-2-en-3-yl] benzenecarbothioate
Molecular formula:	C ₁₉ H ₂₃ N ₄ O ₆ PS
Molecular weight:	466.4 g/mol
Structural formula:	



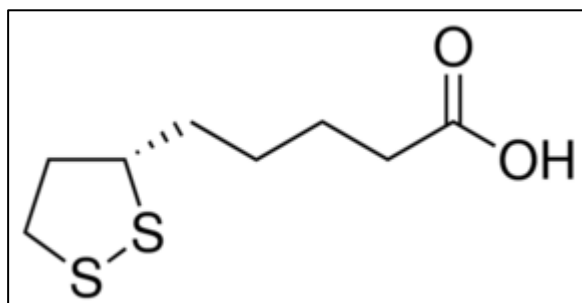
Physicochemical properties:

Appearance & Physical State:	shinning black powder
Density:	1.444 g/cm ³
Melting Point:	165°C
Boiling Point:	745.1°C at 760 mmHg
Flash Point:	404.4°C
Refractive Index:	1.645
Storage Condition:	2-8°C
Vapor Pressure:	2.55E-23mmHg at 25°C

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Alpha Lipoic Acid
Chemical name:	5-[(3R)-dithiolan-3-yl] pentanoic acid
Molecular formula:	$C_8H_{14}O_2S_2$
Molecular weight:	206.3 g/mol
Structural formula:	



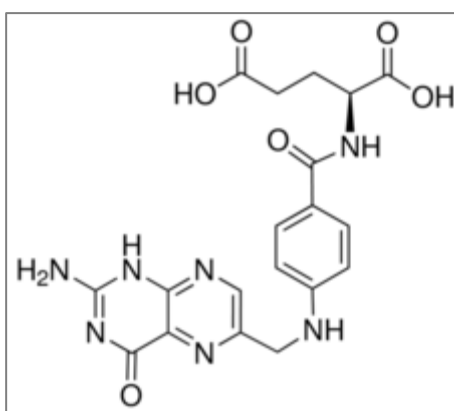
Physicochemical properties:

Physical form:	Solid
Solubility:	Insoluble in water
Melting Point:	Approximately 60.5 Deg °C

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Folic Acid
Chemical name:	(2S)-2-[[4-[(2-amino-4-oxo-3H)-pteridin-6-yl)methylamino]benzoyl]amino]pentanedioic acid
Molecular formula:	C ₁₉ H ₁₉ N ₇ O ₆
Molecular weight:	441.404 g/mol
Structural formula:	



Physicochemical properties:

Physical form:	Yellowish-orange crystals; extremely thin Platelets.
Solubility:	Almost insoluble water, Slightly sol in methanol, less in ethanol and butanol, Soluble in hot dil HCl and H ₂ SO ₄
pKa:	3.5
Melting Point:	Approximately 250 dec °C

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Pyridoxine Hydrochloride
Chemical name:	4,5-bis(hydroxymethyl)-2-methylpyridin-3-ol;hydrochloride
Molecular formula:	$C_8H_{12}ClNO_3$
Molecular weight:	205.638 g/mol
Structural formula:	



Physicochemical properties:

Physical form:	White Crystalline Powder.
Solubility:	Pyridoxine Hydrochloride is freely soluble in water (approx. 20 g per 100 mL), slightly soluble in ethanol, and insoluble in ether and chloroform.
pKa:	5.58 (Strongest Basic)
Melting Point:	Approximately >207°C

PHARMACEUTICAL INFORMATION

PART III: CONSUMER INFORMATION

1. Methylcobalamin / Mecobalamin

What does Vitamin B12 do?

Vitamin B12 helps keep the nervous system and blood cells healthy and prevents a type of anaemia called megaloblastic anaemia. In megaloblastic anaemia the red blood cells are bigger than they should be and there are fewer of them, so they do not carry oxygen around the body as well as they should.

What is Vitamin B12 deficiency?

Vitamin B12 deficiency is when your vitamin B12 levels are too low.

What are the symptoms of Vitamin B12 deficiency?

- Symptoms related to anaemia include - extreme tiredness (fatigue); lack of energy (lethargy); breathlessness; feeling faint; headaches; pale skin; noticeable heartbeats (palpitations); hearing sounds coming from inside the body, rather than from an outside source (tinnitus); loss of appetite and weight loss.
- It is also possible to have vitamin B12 deficiency without having anaemia. You may have B12 deficiency if you have symptoms such as pins and needles; disturbed vision; a sore and red tongue; mouth ulcers; muscle weakness; psychological problems such as depression and confusion; problems with memory, understanding and judgement.
- Because the body stores of vitamin B12 can last for 2-4 years it can take a long time for symptoms to develop so they can happen very gradually and can go un-noticed until levels in the body are quite low.

Where do I get vitamin B12?

Vitamin B12 is only naturally found in animal products including fish, meat, poultry, eggs, milk, and milk products. Vitamin B12 is not generally present in plant foods, but many foods are fortified with B12 including breakfast cereals, soya drinks, and yeast extracts such as marmite.

Who is at risk of vitamin B12 deficiency?

Older adults are more at risk of low vitamin B12 levels. Around 5% of 65 to 74 year-olds, and more than 10% of people over 75 Yrs have low vitamin B12 levels.

Causes of Vitamin B12 deficiency

Some people are not able to absorb vitamin B12 from food and some people have a dietary deficiency of vitamin B12, especially if they do not eat meat. Some medications can also reduce absorption of vitamin B12 from the stomach e.g. the antidiabetic medicine metformin, or medicines for stomach problems such as omeprazole or lansoprazole.

Treatment of Vitamin B12 deficiency

To check whether B12 deficiency is related to diet, take B12 capsule called Methylcobalamin for a few weeks and then perform a blood test to check your B12 levels. If your B12 levels have improved, changing your diet can help treat the condition and prevent it coming back.

Where do I get more information about vitamin B12 deficiency?

Speak to your Physician if you have any concerns about the level of vitamin B12 you get from your diet or you are concerned that you may have symptoms of B12 deficiency.

2. Benfotiamine

What is Benfotiamine?

Benfotiamine is a medication which has benfotiamine as active ingredients present in it. This medicine performs its action by increasing the production of Vitamin B1 in the body. Benfotiamine is used to avoid Wernicke Encephalopathy, beri-beri and Dietary deficiency. It is used to treat conditions such as Neuropathy and cardiovascular disorders.

What are the uses of Benfotiamine?

Benfotiamine is used for the treatment and prevention from conditions and symptoms of diseases like Wernicke Encephalopathy, beri-beri and Dietary deficiency. Besides these, it can also be used to treat conditions like Neuropathy and cardiovascular disorders. The patient should inform the doctor about any ongoing medications and treatment before using Benfotiamine to avoid undesirable effects.

What are the Side Effects of Benfotiamine?

This is a list of possible side-effects which may occur due to the constituting ingredients of Benfotiamine. This is not a comprehensive list. These side-effects have been observed and not necessarily occur. Some of these side-effects may be serious. These include weight gain, skin rashes, itching and irritation. Apart from these, using Benfotiamine may further lead to nausea, vomiting, cough and swollen facial features. If any of these symptoms occur often or on daily basis, a doctor should be urgently consulted.

What are the instructions for storage and disposal Benfotiamine?

Benfotiamine should be stored at room temperature, away from heat and direct light. Keep it away from the reach of children and pets. A doctor should be consulted regarding the dosage of Benfotiamine. The patient should consult a doctor for its further uses and side effects and should inform the doctor about any ongoing medications and treatment before using to avoid undesirable effects.

3. Folic Acid

What is Folic acid used for?

- Folic acid is a vitamin needed by the body to manufacture red blood cells. An insufficient amount of this vitamin causes diseases known as macrocytic or megaloblastic anaemia. These diseases are most likely to occur in children and pregnant women.
- Folic acid may reduce the incidence of neural tube defects (abnormal development of brain and spinal cord) of the baby.
- Additional amount of folic acid may be required when a patient takes excessive amounts of alcohol or when a patient suffering from chronic kidney diseases that attack the red blood cells and break them down.

- Patients taking medications to treat certain disease, such as seizures or malaria and women taking birth control pills also may require more folic acid than their normal diets provide.

What is the role of Folic Acid in Diabetic Neuropathy?

Diabetic Neuropathy involves nerve injury due to chronic hyperglycaemia. Folic Acid improves the expression of Nerve Growth Factor (NGF) and lowers Malonaldehyde (MDA) levels that prevents nerve injury and helps in nerve growth.

When should it be used?

- Usually this medication is taken daily. Your doctor has determined how often and how long you should take this medication.
- To reduce the risk of neural tube defects, folic acid supplements at a daily dose of 5mg can be taken during the first twelve weeks of pregnancy, or even when you are preparing your body for pregnancy.
- In combination with Methylcobalamin, folic acid has found to be very useful in reducing the pain in neuropathy.

What should I do if I miss a dose?

Take the missed dose as soon as you remember it. However, if you remember a missed dose at the time you are scheduled to take the next dose, omit the missed dose completely and continue following your regular medication schedule. Do not take two doses at once.

What side effects can this medicine cause? What can I do about them?

Rash, itching, and difficulty in breathing may rarely occur. Contact your doctor.

Other Precautions?

- Your doctor will want to monitor your response to this medication and may want to change the amount you are to take. Therefore, keep in touch with your doctor while you are taking it.
- This medication may affect the way the body reacts to certain other drugs. Inform your doctor or pharmacist if you intend to take other medications while on folic acid.
- If you are pregnant and if you are receiving anticoagulant therapy or are deficient in Vitamin B12, please see your doctor before starting folic acid supplementation.
- Do not allow anyone else to take this medication.

Special instructions

- Do not stop taking this medication until your doctor tells you to do so.
- If you are planning a pregnancy, you could eat more folate-rich food (eg. Brans and breakfast cereal fortified with folic acid) and avoid overcooking vegetables.
- Storage condition
- Keep this medication in the container it came in and store the container at room temperature and away from direct sunlight.
- Keep this medication out of reach of children.

4. Pyridoxine Hydrochloride

Why is this drug prescribed?

- Pyridoxine is a water-soluble B complex vitamin naturally present in many foods. It is an important vitamin used by the body to prevent seizures and symptoms of peripheral neuropathy (which is characterized by a tingling sensation or numbness in the hands and feet.)
- Some drugs like isoniazid (Isotamine), used in the prevention and treatment of tuberculosis, can cause pyridoxine deficiency.
- As well, some conditions such as alcoholism, diabetes, and malnutrition may increase the risk for peripheral neuropathy and the need for pyridoxine. Therefore, this drug is used as a supplement to prevent symptoms of pyridoxine deficiency.

What is the role of Pyridoxine Hydrochloride in Diabetic Neuropathy?

In diabetic neuropathy, the rate of synthesis of inhibitory neurotransmitters (chemicals like Gamma Amino Butyric Acid) is altered. B₆ improves the Synthesis of key signalling molecules in the nervous system: that helps in reducing the nerve pain.

How should this drug be taken?

- Pyridoxine is available as a 3 mg in MYELOGEN FORTE NU Capsule. Pyridoxine requirements are increased during pregnancy and breastfeeding and also in patients taking birth control or hormone replacement therapy.
- Do not take a higher dose than what is prescribed, since high doses can sometimes cause symptoms of peripheral neuropathy.
- Capsules should be swallowed with water or some other non-alcoholic drink and can be given with or without food.

What should you do if you forget a dose?

If you miss a dose of pyridoxine, take it as soon as possible. However, if it is time for your next dose, do not double the dose; just carry on with your regular schedule.

What adverse effects can this drug cause? What should you do about them?

- Adverse effects such as nausea, stomach upset, headache, and drowsiness have been reported with this drug. If these effects occur and are bothersome, please inform your doctor or pharmacist.
- The long-term effects of this drug, if high doses are taken, may include numbness of hands and feet. If you are concerned about any unexpected effects, please talk to your doctor or pharmacist.

Clinical Trial:

1. A prospective, open-label study on 48 adult diabetic subjects with polyneuropathy who were given 1500 µgm/day of oral methylcobalamin over 24-weeks has shown significant decline in the Toronto CSS score ($p < 0.0001$) indicating improvement in pain score. The symptoms that improved compared to baseline and that did not emerge over the course of 24 weeks were tingling ($p < 0.03$), upper limb symptoms ($p < 0.003$), ataxia ($p < 0.004$), and signs of im-paired position ($p < 0.009$) sense, vibration sense ($p < 0.0001$), pinprick sensation ($p < 0.004$) and knee reflex ($p < 0.004$). Thus, this open label study demonstrated that symptoms of neuropathy significantly improved among subject with DPN treated with methylcobalamin 1500 µgm/day. In addition, new symptoms did not emerge over the 24 weeks observation period.

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You should know that the usual signs of adverse effects that may be associated with MYELOGEN FORTE NU are:

Dizziness, sleepiness, blurred vision, dry mouth, swelling of the extremities, weight gain, trouble concentrating, lack of energy, muscle weakness

Please advise the patients to report for any of the above signs after administration of MYELOGEN FORTE NU.

This product monograph, prepared for health professionals can be found at:

www.panaceabiotec.com or by contacting the Panacea Biotec Limited (INDIA)

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