PRESCRIBING INFORMATION: NEUROBION αLFA D

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NEUROBION αLFA D

Alpha Lipoic acid, Pyridoxine Hydrochloride, Mecobalamin, Folic Acid and Vitamin D3 Tablets

COMPOSITION

Each Film Coated Tablet contains**:**

Alpha Lipoic Acid Coated Equivalent to	
Alpha Lipoic Acid IP ……	100 mg
Pyridoxine Hydrochloride IP ……	3 mg
Mecobalamin IP ……	1500 mcg
Folic Acid IP ……	1.5 mg
Vitamin D3 stabilized equivalent to	
Vitamin D3 IP …….	1000 IU
Excipients	q.s.
Colours ……	Ferric Oxide Red USP NF, Titanium Dioxide IP

Appropriate overages of vitamins added

Excipients used:

1. Colloidal Silicon Dioxide IP
2. Lactose IP
3. Sodium Starch Glycollate IP
4. Maize Starch IP
5. Polyvinyl Pyrrolidone (K-30) IP
6. Magnesium Stearate IP
7. Purified Talc Talcum IP
8. Microcrystalline Cellulose Avicel (PH 112) IP
9. Croscarmellose Sodium IP
10. Isopropyl Alcohol BP
11. Dichloromethane BP (Methylene Chloride)
12. Coating material (Instamoistshield Brown-IC-MS-5238 IH)

PHARMACEUTICAL FORM

Neurobion αlfa D is a Film Coated Tablet containing Mecobalamin, Alpha Lipoic Acid, Folic Acid, Pyridoxine Hydrochloride and Vitamin D3 as active ingredients.

PHARMACOLOGICAL PROPERTIES

PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group:

Mecobalamin: Vitamin B12 analogue

Alpha Lipoic Acid: Antioxidant

Folic Acid: Vitamin B group

Pyridoxine Hydrochloride: Vitamin B6 analogue, water-soluble vitamin

Vitamin D3: Fat soluble vitamin

Therapeutic indication:

- For the treatment of diabetic peripheral neuropathy (DPN)

Posology and method of administration:

One tablet once daily.

MECHANISM OF ACTION:

- **Mecobalamin:**

Mecobalamin is an analog of vitamin B12 which treats or prevents the pathology arising from the deficiency of vitamin B12. Mecobalamin is active in the central nervous system outside the mitochondrion and is essential for cell growth and replication. Through enhanced methylation, it exerts its nerve cell protective effect and accelerates its growth. Mecobalamin is the only form of vitamin B12 that can cross the blood brain barrier without biotransformation. Its methyl group stimulates serotonin creation, a neurotransmitter which is responsible for mood enhancement and protects the brain from damage against excitotoxins.

The oxidizing properties of ROS can cause molecular damages (lipid peroxidation, protein inactivation and DNA breakdown), eventually leading to many chronic diseases including T2DM and diabetic complications. This imbalance leads to damage of important cellular biomolecules with potential adverse effects on organ functions of the whole organism. Several studies suggested that Hyperhomocysteinemia is a pathological metabolite marker for oxidative stress and for T2DM. High homocysteine level is the main culprit for brain, vascular diseases, stroke risk and causes sclerosis in the arteries. Mecobalamin converts homocysteine to methionine and reduces the potential of damage. It also forms adenosylcobalamin, the other form of vitamin B12 for mitochondrial energy production. Along with mecobalamin, 5-methyltetrahydrofolate is also an important element to eliminate homocysteine. Vitamin supplements reduce the chances of building homocysteine associated with stress. It also increases the available amount of SAMe (S-

adenosylmethionine), which acts as a mood enhancer and works as an effective alternative to tricyclic antidepressant.

- **Alpha Lipoic Acid:**

Lipoic acid (LA) or Alpha lipoic acid (ALA) is a naturally occurring compound that is also known as 1,2-dithiolane-3-pentanoic acid or thioctic acid. Alpha lipoic acid increases glucose uptake in insulin-sensitive and insulin-resistant muscle tissues. Mechanistic studies on the effects of alpha lipoic acid on the redox status of insulin responsive cells revealed that alpha lipoic acid stimulates glucose uptake by affecting components of the insulin signalling pathway. Studies on muscle cell lines have indicated that exposure to alpha lipoic acid stimulates glucose uptake by the redistribution of glucose transporters to the plasma membrane, and tyrosine phosphorylation of insulin receptor substrate-1 (IRS-1). In T2DM, there is evidence that alpha lipoic acid ameliorates insulin resistance and impaired glucose metabolism in the periphery. Alpha lipoic acid may intercept with the insulin-signalling pathway by directly or indirectly (through the induction of intracellular ROS) oxidizing components of the insulin-signalling cascade. Alpha lipoic acid was found to stimulate glucose uptake and the increase in glucose uptake was accompanied by rapid translocation of the glucose transporters GLUT4 from an internal membrane fraction to the plasma membrane. Similar to insulin, treatment with alpha lipoic acid results in increased tyrosine phosphorylation of the insulin receptor (IR) and insulin receptor substrate-1 (IRS-1). Alpha lipoic acid is often referred to as an insulinomimetic agent. Extensive evidence suggests that alpha lipoic acid has potential therapeutic value in lowering glucose levels in diabetic conditions and that the intracellular redox status plays a role in the modulation of insulin action and insulin resistance.

Mechanisms that may account for lipoic acid's benefit in preventing diabetic complications include prevention of protein glycosylation and inhibition of the enzyme aldose reductase, the latter of which subsequently inhibits conversion of glucose and galactose to sorbitol. Accumulation of sorbitol has been implicated in the pathogenesis of various diabetic complications, including "sugar cataracts" where sorbitol accumulates in the lens.

- **Folic acid:**

Increased plasma level of homocysteine is a risk factor for cognitive dysfunction and dementia in diabetes. Homocysteine (Hcy) is a sulfur-containing amino acid that is generated during methionine metabolism. It has a physiologic role in DNA metabolism via methylation, a process governed by the presentation of folate, and vitamins B6 and B12. Physiologic Hcy levels are determined primarily by dietary intake and vitamin status. Elevated plasma levels of Hcy (hyperhomocysteinemia) can be caused by deficiency of either vitamin B12 or folate, or a combination thereof. There is evidence from laboratory and clinical studies that Hyperhomocysteinemia exerts direct toxic effects on both the vascular and nervous systems. Recent experimental and clinical studies confirm role of Hyperhomocysteinemia in various neurologic conditions, including stroke, minimal cognitive impairment, dementia, Parkinson's disease, multiple sclerosis, epilepsy and peripheral neuropathy. Recent clinical studies have revealed that Hyperhomocysteinemia exaggerates the prevalence of peripheral neuropathy in diabetics and exacerbates any pre-existing diabetic neuropathy.

Hyperhomocysteinemia might be attributed to the decreased expression or activity of 5',10' methylene tetrahydrofolate reductase (MTHFR) which utilizes folate to regenerate methionine from homocysteine. The metabolism of homocysteine plays an important role in the development of cognitive dysfunction. MTHFR catalyzes the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which serves as a methyl donor in the

reaction converting homocysteine to methionine. A common MTHFR gene mutation C677T results in decreased activity of the MTHFR enzyme. It has been reported that MTHFR C677T mutation results in the increase of serum homocysteine level which is bad for cognitive function. The decreased MTHFR might at least partially contribute to diabetic cognitive dysfunction. Low folate status is associated with poor cognitive function and dementia in the elderly. The supplementation with folic acid for a long term appears to reduce the rate of cognitive decline in older adults.

The absorption of folic acid and vitamin B12 is importantly decreased by the prolonged use of metformin, which is the first-choice drug in uncomplicated diabetes, thus these two nutrients have been found deficient in the disease and most probably need to be supplemented regularly. Patients using metformin during prolonged periods may need folic acid and vitamin B12.

Folate and vitamin B12 treatment is found to improve the insulin resistance and endothelial dysfunction, along with decreasing homocysteine levels, in patients with metabolic syndrome, suggesting that folic acid has several beneficial effects on cardiovascular disease risk factors.

- **Pyridoxine hydrochloride (Vitamin B6):**

Vitamin B6 (pyridoxine, pyridoxal, and pyridoxamine) forms are readily absorbed by passive diffusion in the jejunum and ileum, while alpha glucosidases are expressed and located in the duodenum. The studies suggest that the blood glucose lowering effect of pyridoxine is possibly due to the α-glucosidase inhibitory activities. Furthermore, pyridoxine has high activity of enzyme inhibition (e.g. sucrase, maltase, and glucoamylase).

Recent clinical studies have revealed that Hyperhomocysteinemia exaggerates the prevalence of peripheral neuropathy (PN) in diabetics and exacerbates any pre-existing diabetic neuropathy. The notion of Hyperhomocysteinemia as an independent variable associated with increased prevalence of diabetic PN has been supported by various clinical studies. It was estimated in a recent study that for each 1-mmol/L increase in Hcy (homocysteine), there is a 7.1% increased risk in diabetic autonomic neuropathy. Increased levels of homocysteine are also considered important biomarkers of cardiovascular diseases. Plasma total homocysteine levels tend to be higher in women with clinical and biochemical deficiency of vitamin B6 and therapy with pyridoxine reduced its level significantly.

Pyridoxine is required for the synthesis of the neurotransmitters, serotonin and noradrenaline, and for myelin formation. It functions as a coenzyme in the metabolism of amino acid, glycogen and spingoid bases.

- **Vitamin D3:**

Active 1,25(OH)2D has both endocrine and autocrine hormone activity. It binds to vitamin D3 receptors in the nucleus of cells and, with a retinoid X receptor (RXR) partner, binds specific regions of DNA named vitamin D3 response elements (VDRE) located in the promoter region of genes. The heterodimeric group then allows the binding of co-activator protein complexes that link the RXR-VDR group to transcription start sites. With most human cells expressing VDRs, 1,25(OH)2D has the potential to alter the function of most tissues in the body. The enzyme responsible for the rate-limiting step for the formation of 1,25D, 1-alpha hydroxylase (CYP27B1), has been found in the pancreas, prostate, breast, macrophages, epidermis, parathyroid gland, and intestines. Other non-VDRE related interactions are being investigated.

Vitamin D3 plays important roles in the metabolism of glucose. It directly stimulates insulin secretion from beta cells of pancreas. It increases intracellular calcium levels, which attenuates insulin synthesis. Also, it improves insulin sensitivity in peripheral muscle and fats cells. T2DM

is a state of chronic low-grade chronic inflammation. Because of anti-inflammatory nature, vitamin D3 exerts beneficial effects on glycaemic control and helps in prevention of complications of T2DM. The pathogenesis of T2DM involves both beta-cell dysfunction and insulin resistance. In-vitro and in-vivo studies suggest an important role for vitamin D3 both in beta-cell function and insulin resistance. Hypovitaminosis D correlates with beta-cell dysfunction and insulin resistance in 126 normoglycemic healthy adults studied with an oral glucose tolerance test (OGTT) and hyperglycaemic clamp.

RATIONALE OF COMBINING MECOBALAMIN (VITAMIN B12), ALPHA LIPOIC ACID, FOLIC ACID, PYRIDOXINE HYDROCHLORIDE (VITAMIN B6) AND VITAMIN D3

A combination of mecobalamin, alpha lipoic acid, folic acid, pyridoxine hydrochloride and vitamin D3 has synergistic effect in the management of the diabetes and its complications. It helps protect the nerves from damage, restores its structural and functional integrity and causes a recovery of function. A combination of neurorestorative, neuro re-energizing, neuroregenerative and antioxidant components which have a proven therapeutic value in neuropathy will be very beneficial in retarding the progress of diabetes mellitus.

This combination is also useful to reduce plasma homocysteine at various levels and thus prevents possible deterioration of vital organs.

This combination of nutrients from vitamin B group is obviously helpful in vitamin B deficiency state. It also increases energy and enthusiasm levels in the subjects.

PHARMACOKINETIC PROPERTIES

Mecobalamin:

Vitamin B12 substances bind to intrinsic factor, a glycoprotein secreted by the gastric mucosa, and are then actively absorbed from the gastrointestinal tract. 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, 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. Vitamin B12 diffuses across the placenta and also appears in breast milk.

Evidence indicates Mecobalamin is utilized more efficiently than cyanocobalamin to increase levels of one of the coenzyme forms of vitamin B12. Experiments have demonstrated similar absorption of mecobalamin following oral administration. 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.

Alpha Lipoic Acid (ALA):

Alpha lipoic acid appears to be readily absorbed from an oral dose and converts easily to its reduced form, dihydrolipoic acid (DHLA), in many tissues of the body. The effects of alpha lipoic acid and DHLA are present both intra- and extracellularly. Alpha lipoic acid contains an asymmetrical carbon and thus has two possible optical isomers. These are designated as R-lipoic

acid (R-ALA) and S-lipoic acid (S-ALA). Naturally occurring alpha lipoic acid is in the R configuration, bound to a protein where it functions as an essential cofactor for several mitochondrial enzyme complexes involved in energy production and the catabolism of alpha-keto acids and amino acids. Nutritional supplements of alpha lipoic acid are typically comprised either of R-ALA alone or a racemic mixture of R-ALA and S-ALA (RS-ALA). Human studies using oral racemic mixtures of alpha lipoic acid have observed plasma concentrations of R-ALA to be greater than that of S-ALA.

Folic acid:

Folic acid is rapidly absorbed from the gastrointestinal tract, mainly from the duodenum and jejunum. Folic acid given therapeutically enters the portal circulation largely unchanged, since it is a poor substrate for reduction by dihydrofolate reductase. It is converted to the metabolically active form 5-methyltetrahydrofolate in the plasma and liver. Human pharmacokinetic studies indicate folic acid has very high bioavailability, with large oral doses of folic acid substantially raising plasma levels in healthy subjects in a time- and dose-dependent manner. Subsequent to high-dose oral administration of folic acid (ranging from 25-1,000 mg/day), RBC folate levels remain elevated for periods in excess of 40 days following discontinuation of the supplement. Folic acid is poorly transported to the brain and rapidly cleared from the central nervous system. The primary methods of elimination of absorbed folic acid are fecal (through bile) and urinary.

Pyridoxine hydrochloride (Vitamin B6):

Pyridoxine and its vitamers, when taken orally, are absorbed in the upper small intestine by simple diffusion and transported to the liver for biotransformation into the active form's pyridoxal phosphate and pyridoxamine phosphate. They are stored mainly in the liver where there is oxidation to 4-pyridoxic acid and other inactive metabolites which are excreted in the urine. As the dose increases, proportionally greater amounts are excreted unchanged in the urine. Uptake into tissue is by extracellular de-phosphorylation, followed by metabolic trapping intracellularly as P5P. Pyridoxal crosses the placenta and is distributed into breast milk.

Vitamin D3:

Due to its metabolism into many inactive and excretable forms, less than 25 percent of vitamin D becomes 25(OH)D. Vitamin D is stored in both muscle and fat tissue, with vitamin D levels in the serum correlated to the amount of D in fat tissue. Studies of radioactively labelled D3 find the whole body half-life of vitamin D3 molecules to be approximately 62 days.

Vitamin D analogues are readily absorbed from the small intestine if fat absorption is normal. Bile is required for absorption. Vitamin D and its metabolites circulate in the blood bound to a specific alpha-globulin. Vitamin D can be stored in adipose and muscle tissue for long periods of time. It is slowly released from such storage sites and from the skin where it is formed in the presence of sunlight or ultraviolet light. Ergocalciferol and cholecalciferol have a slow onset and a long duration of action; calcitriol and its analogue alfacalcidol, however, have a more rapid action and shorter half-lives.

Cholecalciferol and ergocalciferol are hydroxylated in the liver by the enzyme vitamin D 25-hydroxylase to form 25-hydroxycolecalciferol (calcifediol) and 25-hydroxyergocalciferol respectively. These compounds undergo further hydroxylation in the kidneys by the enzyme vitamin D 1-hydroxylase to form the active metabolites 1,25-dihydroxycolecalciferol (calcitriol) and 1,25-dihydroxyergocalciferol respectively. Further metabolism also occurs in the kidneys, including the formation of the 1,24,25-trihydroxy derivatives. Of the synthetic analogues, alfacalcidol is converted rapidly in the liver to calcitriol, and dihydrotachysterol is hydroxylated, also in the liver, to its active form 25-hydroxydihydrotachysterol.

Vitamin D compounds and their metabolites are excreted mainly in the bile and faeces with only small amounts appearing in urine, there is some enterohepatic recycling, but it is considered to have a negligible contribution to vitamin D status. Certain vitamin D substances may be distributed into breast milk.

CLINICAL EFFICACY:

B group-vitamins are natural tonic health vitamins that nourish nerves and muscles and also improve appetite.

Clinical and biochemical vitamin B12 deficiency is highly prevalent among patients with both types 1 and 2 DM. Vitamin B12 supplementation and optimal supplementation dose among type-1 and type-2 diabetic patients are warranted to help guide formulation of guidelines in diabetes clinical care. Annual screening for vitamin B12 deficiency using more sensitive methods like serum homocysteine and methylmalonic acid concentrations (in clinical settings where they are accessible) and supplementation should be adopted among diabetic patients with specific risk factors of vitamin B12 deficiency.

Vitamin B12 deficiency and the accompanying Hyperhomocysteinemia and elevated MMA levels have been documented to cause a distinct sensory polyneuropathy that closely mimics diabetic neuropathy. Worsening of diabetic neuropathy is also noted among patients with co-existing vitamin B12 deficiency.

Many clinical studies validate that alpha lipoic acid (ALA) is one of the most promising natural treatments for diabetes. Alpha lipoic acid is potent anti-oxidants and has been shown to significantly reduce the symptoms of neuropathy. It has also been shown to improve insulin sensitivity by recruiting glucose transporter-4 to plasma membranes causing uptake of glucose. New studies have also suggested that alpha lipoic acid stimulates glucose disposal in patients with T2DM. In experimental and clinical studies, alpha lipoic acid markedly reduced diabetic pathologies including cataract formation, vascular damage and polyneuropathy.

Alpha lipoic acid reduces the activity of the kinase protein activated by the AMP (AMPK) and works as a sensor in the cell activated when cell energy is reduced. The activation of hypothalamic AMPK reverts the effects of alpha lipoic acid in the intake of food and the release of energy. Hyperphagia induced by 2 deoxy glucose is reversed by the AMPK inhibition. Hypothalamic AMPK is important in the central regulation of food intake and energy release and alpha lipoic acid excerpts anti-obesity effects through the suspension of such activity in the hypothalamic AMPK.

A double-blind randomized controlled clinical trial was performed to determine the effects of supplementation of folate on indices of glycaemic control, insulin resistance and lipid profile in men with T2DM, showed that, a pharmacological dose of folic acid supplementation decreased plasma level of homocysteine and improved glycaemic control, insulin resistance and folate levels, a finding which suggests a safe and inexpensive therapy for lowering homocysteine and improving the overall management of diabetic patients.

The treatment with pyridoxine on plasma total homocysteine concentration in 20 women with clinical and biochemical deficiencies of pyridoxine, showed that plasma total homocysteine levels tended to be higher in women with clinical and biochemical deficiency of vitamin B6 and therapy with pyridoxine reduced its level significantly.

The studies have shown the possible relation between vitamin D deficiency and diabetic peripheral neuropathy. Vitamin D deficiency found highly prevalent in diabetic peripheral

neuropathy patients. Females and patients with severe form of neuropathy are more liable for lower vitamin D levels.

Recently, increasing studies have been carried out to explore the association between vitamin D level and the development of diabetic peripheral neuropathy (DPN) in patients with diabetes mellitus (DM). The meta-analysis indicates that vitamin D deficiency is associated with the generation and development of DPN in Caucasians with T2DM. In Asian diabetic patients, those with vitamin D deficiency are 1.22 times more prone to suffer from DPN compared with those having normal vitamin D level. Vitamin D3 supplementation is urgently needed in these patients to prevent the development of DPN in T2DM.

A large population-based study has recently shown that the prevalence of painful diabetic neuropathy (PDN) is ~21%, and painful symptoms are more prevalent in patients with type 2 diabetes, females, and South Asians. A recent case report on a patient with painful diabetic neuropathy who had been refractory to treatment with tricyclic's, gabapentin, pregabalin, and oxycodone, showed a dramatic improvement in neuropathic symptoms after treatment with 50,000 IU of vitamin D2 weekly. Furthermore, recently, a placebo-controlled trial of oral vitamin D3 in type 2 diabetes has shown a significant reduction in the Neuropathy Symptom Score with no change in the NDS or neurophysiology.

Vitamin D3 adequacy is evaluated by measuring serum 25(OH)D concentration, as this is the primary circulating form of vitamin D. Serum 25(OH)D is inversely associated with haemoglobin A1c (HbA1C) especially at concentrations less than 65 nmol/l and in participants with higher BMI. Hypovitaminosis D is more prevalent in patients with T2DM than in those without and is associated with increased diabetes prevalence and insulin resistance assessed by fasting glucose and insulin levels. Similarly, a significant inverse association was observed between serum 25(OH)D concentration and T2DM. In another study, baseline 25(OH)D was found inversely associated with 10-year risk of hyperglycaemia (fasting glucose and 2 h post-OGTT) and insulin resistance.

PRECLINICAL SAFETY DATA:

Toxicity

Mecobalamin: Vitamin B12 has been considered of very low toxicity by several international bodies. According to the Scientific Committee on Food (SCF; EC, 2000), "no adverse effects have been associated with excess vitamin B12 intake from food or supplements in healthy individuals. Vitamin B12 has a history of safe long-term use as a therapeutic agent given in high dosages per oral, or via intramuscular injections, for treatment of disorders associated with impaired vitamin B12 absorption, such as in gastrectomy and malabsorption. In vitamin B12 replacement therapy oral or intramuscular dosages between 1,000–5,000 µg vitamin B12 are used, with no supportive evidence of adverse effects up to at least 5 years.

Alpha lipoic acid: Alpha lipoic acid appears to be safe in dosages generally prescribed clinically. The LD50 was 400-500 mg/kg after an oral dosage in dogs however, lower dosages (20 mg/kg) given intraperitoneally to severely thiamine-deficient rats proved fatal. Anecdotal evidence suggests alpha lipoic acid may be hepatotoxic to cats at doses greater than 20 mg daily. Allergic skin conditions are among the few reported side effects of lipoic acid administration in humans.

Folic acid: In doses typically administered for therapeutic purposes, folic acid is considered non-toxic. At doses of 15 mg daily and above, gastrointestinal complaints, insomnia, irritability, and fatigue have been mentioned as occasional side effects. Folic acid is considered safe during

pregnancy, with an established recommended intake of 800 mcg daily. Some animal studies have shown that folic acid can be a neurotoxin and can cause convulsions in laboratory animals. This evidence is in part based upon in vitro tissue and cell culture studies, and/or using very high dose levels (i.v. dosages 60-90 mg).

Pyridoxine hydrochloride (Vitamin B6): The use of supplemental pyridoxine hydrochloride has not been associated with toxicity, although the inactive form, pyridoxine, has been associated with reports of peripheral neuropathy. One hypothesis is that pyridoxine toxicity is caused by exceeding the liver's ability to phosphorylate pyridoxine to P5P, yielding high serum levels of pyridoxine which may be directly neurotoxic or may compete with P5P for binding sites, resulting in a relative deficiency. The electrophysiological and neurological examination of 17 homocysteinuric patients who had been treated with 200-500 mg pyridoxine HCl daily for 10-24 years, and found no evidence of neuropathy. Most reported cases of neuropathy associated with pyridoxine supplementation have involved intake of at least 500mg/day for two years or more. While there is no doubt that vitamin B6 (pyridoxine hydrochloride) can be neurotoxic in gross excess, there is considerable controversy over the way in which toxicological data have been translated into advised limits.

Vitamin D3:
Vitamin D toxicity, also called hypervitaminosis D, is a rare but potentially serious condition that occurs when an individual is exposed to excessive amounts of vitamin D for prolonged period of time. Vitamin D toxicity is usually caused by mega doses of vitamin D3 supplements, not by diet or exposure to the sun. This is because the human body regulates the amount of previtamin D produced by UVB, and even fortified foods do not contain large amounts of vitamin D.

Some define vitamin D toxicity as the presence of hypercalcemia (>2.75 mmol/L on one occasion) and an elevated 25(OH)D level (>150 ng/mL). Urinary calcium: creatinine ratios >1 often precede hypercalcemia. Common symptoms of hypervitaminosis D and hypercalcemia are anorexia, weight loss, weakness, fatigue, disorientation, vomiting, dehydration, polyuria, constipation, fever, chills, abdominal pain, and renal dysfunction.

Carcinogenicity and genotoxicity

Mecobalamin: There is no evidence from the long-term use in patients with pernicious anaemia that this compound is carcinogenic (FDA, 2014). No studies have investigated the reproductive or developmental toxicity of vitamin B12. In humans, the acute toxicity seems very low.

Alpha Lipoic Acid: Carcinogenicity study in rats administered with 20,60 or 180mg/kg b.w./day alpha lipoic acid for 24 months showed no toxicological significant changes. No indication of genetic mutations was found in genotoxic study. Alpha lipoic acid administration, in conjunction with cyclophosphamide, lowered the toxic effects of anticancer drugs when tested in animals. There were no indications of genetic or chromosomal mutations in mutagenic potential studies.

Folic acid: Folic acid has been associated with an increased incidence of oropharynx, hypopharynx and all cancers, but, in other (observational) studies an inverse relation was found between folate intake and/or status and colorectal cancer and with cervical cancer. Treatment of smokers with 10 mg folic acid plus 500 µg hydroxocobalamin for 4 months resulted in a reduction in atypical bronchial squamous metaplasia.

Pyridoxine hydrochloride (Vitamin B6): There is no evidence from the long-term use of large doses of pyridoxine that this compound is carcinogenic.

Vitamin D3: No long-term animal studies have been performed to evaluate the drug's potential in these areas.

CLINICAL PARTICULARS:

Contraindications:

Neurobion αlfa D is contraindicated in patients with known hypersensitivity to either of the active substances or any of the excipients. Neurobion αlfa D contraindicated in patients with cobalt hypersensitivity because Mecobalamin contains cobalt. Individuals who have diseases of the small intestine, especially Crohn's disease and Sprue, may have trouble absorbing folic acid. Neurobion αlfa D also contraindicated in hypercalcaemia, hypervitaminosis D, arteriosclerosis or cardiac function impairment, renal function impairment, sarcoidosis, and possibly other granulomatous diseases (increased sensitivity to effects of vitamin D).

Side effects:

Immune system disorders (frequency not known): Hypersensitivity reactions, such as sweating, tachycardia, and skin reactions with itching and urticaria

Gastrointestinal disorders (frequency not known): Gastrointestinal complaints, such as nausea, vomiting, diarrhoea and abdominal pain

Renal and urinary disorders (frequency not known): Chromaturia ('reddish urine') appeared during the first 8 hours after an administration and typically resolves within 48 hours.

Special warnings and precautions for use:

This combination is not suitable for use in children under the age of 14 years.

It is advisable to avoid its usage in the individuals who are hypersensitive to any of the ingredients.

The prolonged use of higher doses of mecobalamin is not recommended for patients whose occupation involves handling of mercury or mercury compounds. Mecobalamin should be used cautiously in patients of hypertension, cardiovascular and lung diseases. Mecobalamin needs to be used cautiously in patients with subnormal levels of potassium, as it may result in fatal hypokalaemia in susceptible individuals.

Diabetes or glucose intolerant patients must be cautioned with the use of alpha lipoic acid as it may lower blood glucose levels. Blood glucose should be monitored, and anti diabetic drug dose adjusted, if necessary, to avoid possible hypoglycaemia.

Folic acid should never be given alone or with inadequate amounts of vitamin B12 for the treatment of undiagnosed megaloblastic anaemia, since folic acid may produce a haematopoietic response in patients with a megaloblastic anaemia due to vitamin B12 deficiency without preventing aggravation of neurological symptoms. This masking of the true deficiency state can lead to serious neurological damage.

Severe sensory neuropathy has been described in patients receiving large doses of pyridoxine (2 to 6 g daily) for periods of 2 to 40 months. There has, however, been debate as to whether smaller doses can produce such effects.

Hypersensitivity to vitamin D3 may be one etiologic factor in infants with idiopathic hypercalcemia. In these cases, vitamin D3 must be strictly restricted.

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 B12 deficiency, which results in higher levels of homocysteine. Moreover, the negative effect of metformin on vitamin B12 levels should be conducted during long term treatment with metformin.

Absorption of vitamin B12 from gastrointestinal tract may be reduced by neomycin, amino-salicylic acid, anticonvulsants, nitrous oxide, potassium chloride, H2 antagonists, omeprazole, colchicine, and excessive alcohol consumption. Serum concentration may be decreased by use of oral contraceptives. Many of these interactions are unlikely to be of clinical significance but should be taken in to account when performing assays for blood concentrations. Parenteral chloramphenicol may alter the effect of vitamin B12 in anemia.

Alpha Lipoic Acid: Alpha lipoic acid is a metal chelating agent and can interact with metal compounds found in drugs or milk product. Hence concomitant use of alpha lipoic acid and iron or magnesium containing products should be avoided. The blood sugar levels must be strictly monitored in diabetic patients using alpha lipoic acid as hypoglycemic effect could be increased. To avoid hypoglycemic effect, the dose of oral Antidiabetic drugs might need to be reduced. Patients with diabetic neuropathy are recommended to avoid alcohol consumption as it may compromise the effects of alpha lipoic acid.

Folic acid: Phenytoin isoniazid, primidone, barbiturates, sulfasalazine, glutethimide, cycloserine, folic acid antagonists (methotrexate, pyrimethamine, triamterene, diamidine compounds, trimethoprim), anticonvulsants, antacids, cholestyramine, colestipol, H2 blockers, carbamazepine, phenobarbital, valproate, sulfasalazine, nitrous oxide, and oral contraceptives decrease absorption of folic acid. Pregnant and lactating women and people undergoing haemodialysis for kidney disease develop this deficiency because they have an increased need for folic acid. When cholestyramine and folic acid are administered together, there may be a reduction or delay in folic acid absorption. If concomitant therapy is required, folic acid should be administered at least one hour before or 4-6 hours after cholestyramine.

Alcohol interferes with the absorption and metabolism of folic acid. Those who drink large amounts of alcohol develop this deficiency. Folic acid may interfere with the action of anticonvulsant drugs. Folic acid therapy in folate-deficient individuals may decrease serum levels of phenytoin.

Pyridoxine hydrochloride (Vitamin B6): The antituberculosis drug isoniazid can result in a functional vitamin B6 deficiency. Anti-parkinsonian drugs benserazide and carbidopa cause vitamin B6 depletion by forming hydrazones. Pyridoxine will reduce the efficacy of levodopa in controlling parkinsonian symptoms, the magnitude of the effect proportional to the dose of pyridoxine. There have been many reports of abnormal tryptophan metabolism in women taking either oral contraceptive or menopausal hormone replacement therapy, which have been interpreted as indicating oestrogen-induced vitamin B6 deficiency or depletion.

Vitamin D3: Hypomagnesemia may develop when magnesium containing antacids are used concurrently with vitamin D, particularly in patients with chronic renal failure. Decreased vitamin D3 effects may occur when certain anticonvulsants such as phenytoin, phenobarbital are administered, as they may induce hepatic microsomal enzymes and accelerate the conversion of vitamin D3 to inactive metabolites.

Patients on cholestyramine or colestipol should be advised to allow as much time as possible between the ingestion of these drugs and Vitamin D. Intestinal absorption of vitamin D3 may be impaired because of these drugs.

Vitamin D3 should be used with caution in patients on digoxin as hypercalcemia (which may result with use of vitamin D) may precipitate cardiac arrhythmias. There is an increased risk of hypercalcaemia if vitamin D3 is co-administered with thiazide diuretics and calcium. Plasma-calcium concentrations should be monitored in patients receiving the drugs concurrently. Different Vitamin D analogues should not be administered concurrently.

Pregnancy and Lactation:

Use during pregnancy and lactation (breastfeeding) should only be considered upon careful benefit/risk assessment.

Mecobalamin: Vitamin B12 is distributed into breast milk. The American Academy of Pediatrics considers its use to be usually compatible with breast feeding.

Folic acid: Pregnant women are more prone to develop folate deficiency which can lead to complications and foetal abnormalities. Folic acid is actively excreted in human breast milk. Adverse effects in breast-fed infants have not been documented intake of normal daily requirements of folic acid during lactation.

Alpha Lipoic Acid: Alpha lipoic acid when administered orally at maximal dose of 68.1mg/kg did not show any influence on the fertility or the early fetus development in rats. In rabbits, no malformations were observed at toxic doses, when applied. Due to lack of sufficient long-term safety data, alpha lipoic acid therapy should be taken only under medical supervision during pregnancy. Use of alpha lipoic acid should be avoided by nursing mother.

Pyridoxine hydrochloride (Vitamin B6): Vitamin B6 is excreted into breast milk. While some have expressed concern over the inhibition of breast milk secretion by pyridoxine, most other experts have cautioned that pyridoxine deficiency may cause seizures in the neonate. The American Academy of Paediatrics considers the use of pyridoxine to be usually compatible with breast feeding.

Vitamin D3: Maternal hypercalcemia, possibly caused by excessive vitamin D3 intake during pregnancy, has been associated with hypercalcemia in neonates, which may lead to supravalvular aortic stenosis syndrome, the features of which may include retinopathy, mental or growth retardation, strabismus and other effects. Hypercalcemia during pregnancy may also lead to suppression of parathyroid hormone release in the neonate, resulting in hypocalcaemia, tetany and seizures.

Overdosage of vitamin D3 has been associated with foetal abnormalities in animals. Animal studies have shown calcitriol to be teratogenic when given in doses 4 and 15 times the dose recommended for human use. Vitamin D is deficient in-maternal milk; therefore, breastfed infants may require supplementation. Use of-excessive amounts of Vitamin D3 in nursing mothers may result in hypercalcemia in infants. Doses of Vitamin D3 in excess of 10 µg daily should not be administered daily to nursing women.

Effects on ability to drive and use of machines:

No specific instructions or precautionary measures are intended for driving the vehicle or working on a machine, when a person is being administered the course of Neurobion αlfa D.

Undesirable effects:

Mecobalamin: Oral consumption of mecobalamin, even in larger doses, is considerably safe. In some cases, hypokalaemia and thrombocytosis has occurred in the patient while treating megaloblastic anaemia with Mecobalamin. Rarely mild side effects like diarrhoea, bloating, allergic reactions including skin rash, itching, dyspnoea, headache, *polycethaemia vera*, transitory exanthema, and swelling of mouth, face, lips or tongue.

Alpha Lipoic Acid: Safety analysis conducted in clinical trials demonstrated a dose dependent increase in nausea, vomiting and vertigo. Clinical trials results indicate that the higher doses (>600mg once daily) resulted in increased rates of gastrointestinal side effects. The adverse effects reported with the use of alpha lipoic acid were eye, skin, gastrointestinal and/or respiratory tract irritation.

Folic acid: Folic acid is generally well tolerated. Gastrointestinal disturbances and hypersensitivity reactions have been reported rarely.

Pyridoxine hydrochloride: Severe sensory neuropathy has been described in patients receiving large doses of pyridoxine (2 to 6 g daily) for periods of 2 to 40 months. There has, however, been debate as to whether smaller doses can produce such effects.

Vitamin D3: Hypervitaminosis D is characterized by impairment of renal function with polyuria, nocturia, polydipsia, hypercalciuria, reversible azotemia, hypertension, nephrocalcinosis, generalized vascular calcification, or irreversible renal insufficiency. Widespread calcification of the soft tissues, including the heart, blood vessels, renal tubules, and lungs are also reported.

Overdose:

Mecobalamin: At a very high dose, mecobalamin causes blood clots, diarrhoea, paraesthesia, rhinitis, ataxia, pruritis and allergic reactions. People with *polycythaemia* should consult a physician before taking this therapy.

Alpha Lipoic Acid: In case of overdose with alpha lipoic acid nausea, vomiting and headache may occur. Severe intoxication cases reported include accidental or intentional intake of 10 to 40 g of alpha lipoic acid in combination with alcohol which may tend to be lethal exhibiting psychomotor excitement and generalized attacks. In case of intoxication, the patient should be hospitalized immediately and treated symptomatically as required.

Folic acid: Folic acid is relatively non-toxic but has rarely caused allergic reactions including erythema pruritus, and urticaria. High doses (e.g. 12 mg/day) have rarely been associated with various gastrointestinal symptoms and CNS effects such as altered sleep patterns, difficulty concentrating, over activity, excitement, mental depression, confusion, and impaired judgment.

Pyridoxine hydrochloride (Vitamin B6): There are no known toxicities associated with pyridoxine hydrochloride in lower doses. However, pyridoxine hydrochloride (vitamin B6) can be neurotoxic when taken in large doses. Several cases have been reported in people taking 2 grams or more per day. Symptoms included tingling in the hands and feet, decreased muscle coordination, and a stumbling gait. All recovered without problems after discontinuing or substantially reducing their intake of the vitamin.

Vitamin D3: Hypervitaminosis D is characterized by hypercalcemia with anorexia, nausea, weakness, weight loss, vague aches and stiffness, constipation, mental retardation, anaemia, and mild acidosis. Impairment of renal function, calcification of the soft tissues, including the heart,

blood vessels, renal tubules, and lungs may occur. Decline in the average rate of linear growth and increased mineralization of bones in infants and children (dwarfism) may be the consequences of overdose of vitamin D.

PHARMACEUTICAL PARTICULARS:

Shelf life: 18 Months

Special precautions for storage:

Store at or below 25^0C in a dry place. Protect from light and moisture.
Keep **the medicine** out of reach of children.

Packing: Blister strip of 10 tablets

Date of creation of Prescribing Information:

December 2022

Manufactured by:

Please refer the pack for manufacturing site details.

Marketed by:

Procter & Gamble Health Limited

(Registered Office): Ground Floor and First Floor,

P&G Plaza, Cardinal Gracious Road,

Chakala, Andheri (East), Mumbai – 400099.