NOVA PLUS Capsules (Pregabalin + Mecobalamin + Alpha-lipoic acid)

Composition

NOVA PLUS 75 Capsules

Each hard gelatin capsule contains:

Pregabalin .....75 mg

Mecobalamin.....750 mcg

Alpha-lipoic Acid.....150 mg

(In film-coated tablet form)

Dosage Form

Capsule

Description

NOVA PLUS is a combination of pregabalin, mecobalamin and alpha-lipoic acid. Pregabalin is a structural derivative of the inhibitory neurotransmitter, gamma-aminobutyric acid (GABA). Pregabalin does not bind directly to $GABA_A$, $GABA_B$, or benzodiazepine receptors, does not augment $GABA_A$ responses in cultured neurons, does not alter rat brain GABA concentration or have acute effects on GABA uptake or degradation. Pregabalin binds with high affinity to the $alpha_2$-delta site (an auxiliary subunit of voltage-gated calcium channels) in central nervous system tissues.

Mecobalamin is a kind of endogenous coenzyme vitamin B_{12}. It is well transported to nerve cell organelles and promotes nucleic acid and protein synthesis, axonal transport, axonal regeneration and myelination.

Alpha-lipoic acid is a natural antioxidant which has a potent antioxidant action in majority of the body tissues. This action helps to protect the nerve cell against reactive decomposition products.

Pharmacology

Pharmacodynamics

Pregabalin

Pregabalin binds with high affinity to the $alpha_2$-delta site (an auxiliary subunit of voltage-gated calcium channels) in central nervous system tissues. Although the mechanism of action of pregabalin is unknown, results with genetically modified mice and with compounds structurally related to

pregabalin (such as gabapentin) suggest that binding to the alpha$_2$-delta subunit may be involved in pregabalin's anti-nociceptive and anti-seizure 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 alpha$_2$-delta containing calcium channel trafficking and/or reducing calcium currents. Evidence from other animal models of nerve damage and persistent pain suggest the anti-nociceptive activities of pregabalin may also be mediated through interactions with descending noradrenergic and serotonergic pathways originating from the brainstem that modulate pain transmission in the spinal cord.

Pregabalin does not block sodium channels, is not active at opiate receptors, and does not alter cyclooxygenase enzyme activity. It is inactive at serotonin and dopamine receptors and does not inhibit dopamine, serotonin, or noradrenaline reuptake.

Mecobalamin

Mecobalamin is a cofactor in the enzyme methionine synthase, which functions to transfer methyl groups for the regeneration of methionine from homocysteine.

Alpha-lipoic acid

Alpha-lipoic acidscavenges superoxide radicals and hydroxyl radicals and prevents lipid peroxidation. Oxygen-derived free radicals produced during biological activation of drugs damage red blood cells, causing aging and haemolysis. It also improves insulin action of skeletal muscle glucose transport and metabolism in human and animal models of insulin resistance.

Pharmacokinetics

Absorption

Pregabalin

Following oral administration of pregabalin under fasting conditions, peak plasma concentrations occur within 1.5 hours. Pregabalin oral bioavailability is ≥90% and is independent of dose. Following single-dose (25–300 mg) and multiple-dose (75–900 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 24–48 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 25–30% and an increase in time at peak concentrations (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.

Mecobalamin

Evidence indicates mecobalamin is utilized more efficiently than cyanocobalamin to increase levels of one of the coenzyme forms of vitamin B_{12}. Experiments have demonstrated similar absorption of mecobalamin following oral administration.

Alpha-lipoic acid

Human pharmacokinetic studies have found that alpha-lipoic acid possesses an extremely short plasma half-life of about 30 minutes after both oral and intravenous administration. Oral lipoic acid is absorbed rapidly and the maximum plasma concentration is reached within 30 minutes to 1 hour

for doses of up to 600 mg. The absolute bioavailability after a single oral dose of 200 mg is approximately 30%.

Distribution

Pregabalin

Pregabalin does not bind to plasma proteins. The apparent volume of distribution of pregabalin following oral administration is approximately 0.5 L/kg. Pregabalin is a substrate for system L transporter which is responsible for the transport of large amino acids across the blood brain barrier. Although there are no data in humans, pregabalin has been shown to cross the blood brain barrier in mice, rats, and monkeys. In addition, pregabalin has been shown to cross the placenta in rats and is present in the milk of lactating rats.

Mecobalamin

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. Cobalamin circulates in plasma bound to two carrier proteins: transcobalamin and haptocorrin.

Alpha-lipoic acid

Even after repeated oral administration of lipoic acid, it appears that accumulation in plasma is not achieved. Presumably, this reflects the short plasma half-life and extensive presystemic elimination, which is thought to be primarily hepatic.

Metabolism and Excretion

Pregabalin

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. In preclinical studies, pregabalin (S-enantiomer) did not undergo racemization to the R-enantiomer in mice, rats, rabbits, or monkeys. Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug, with a mean elimination half-life of 6.3 hours in subjects with normal renal function. Mean renal clearance was estimated to be 67.0 to 80.9 mL/min in young healthy subjects. Because pregabalin is not bound to plasma proteins this clearance rate indicates that renal tubular reabsorption is involved. Pregabalin elimination is nearly proportional to creatinine clearance (CLcr).

Mecobalamin

Human urinary excretion of mecobalamin is about one-third that of a similar dose of cyanocobalamin, indicating substantially greater tissue retention. Approximately, 40–90% of the cumulative amount of total cobalamin is excreted within the first 8 hours in the urine.

Alpha-lipoic acid

Following oral lipoic acid administration, a maximum plasma level is quickly reached, but it falls just as quickly to a level insufficient to impact insulin sensitivity or glucose control. Important metabolites of alpha-lipoic acid identified are dihydrolipoic acid, bisnorlipoic acid, 13-

hydroxybisnorlipoic acid and tetranorlipoic acid. All the metabolites possess anti-oxidant activity. The main metabolite excreted in the urine is found to be S^4,S^6-dimethylbisnorlipoic acid.

Special Populations

Geriatric

Oral clearance of pregabalin tended to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with age-related decreases in CLcr. Reduction of pregabalin dose may be required in patients who have age-related compromised renal function. Pharmacokinetics of alpha-lipoic acid and mecobalamin in geriatrics is not known.

Gender

Population pharmacokinetic analyses of the clinical studies showed that the relationship between daily dose and pregabalin drug exposure is similar between genders. Pharmacokinetic differences of alpha-lipoic acid and mecobalamin between genders is not known.

Renal Impairment and Haemodialysis

Renal clearance of pregabalin is nearly proportional to CLcr. Dosage reduction in patients with renal dysfunction is necessary. Pregabalin is effectively removed from plasma by haemodialysis. Following a 4-hour haemodialysis treatment, plasma pregabalin concentrations are reduced by approximately 50%. For patients on haemodialysis, dosing must be modified.Pharmacokinetics of alpha-lipoic acid and mecobalamin in patients with renal impairment or haemodialysis is not known.

Paediatrics

Pharmacokinetics of pregabalin and mecobalamin has not been adequately studied in paediatric patients. Also, children and adolescents must not be treated with alpha-lipoic acid as there is insufficient experience with this age group.

Race

In population pharmacokinetic analyses of the clinical studies in various populations, the pharmacokinetics of pregabalin were not significantly affected by race (Caucasians, Blacks, and Hispanics).Pharmacokinetic differences of alpha-lipoic acid and mecobalamin between races is not known.

Indication

NOVA PLUS is indicated for management of neuropathic pain associated with diabetic peripheral neuropathy.

Dosage and Administration

NOVA PLUS is given orally with or without food.

Dosing should begin at 2 capsules per day divided in two doses and may be increased within 1 week based on efficacy and tolerability to a total of 4 capsules per day given in divided doses (2-3 times/day). Because pregabalin is eliminated primarily by renal excretion, the dose should be adjusted for patients with reduced renal function.

Although pregabalin was also studied at 600 mg/day, there is no evidence that this dose confers additional significant benefit and this dose was less well tolerated. In view of the dose-dependent adverse effects, treatment with doses above 300 mg/day of pregabalin are not recommended. The maximum recommended dose of **NOVA PLUS** is 4 capsules per day in patients with CLcr of at least 60 mL/min.

When discontinuing **NOVA PLUS**, taper gradually over a minimum of one week.

Patients with Renal Impairment

In view of dose-dependent adverse reactions and since pregabalin is eliminated primarily by renal excretion, the dose should be adjusted in patients with reduced renal function. Dosage adjustment in patients with renal impairment should be based onCLcr, as indicated in Table 1 below. Creatinine clearance in mL/min may be estimated from serum creatinine (mg/dL) determination using the Cockcroft and Gault equation:

$$\text{CLcr} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \ (\times 0.85 \text{ for female patients})$$

Table 1: Pregabalin Dosage Adjustment Based on Renal Function

Creatinine Clearance (CLcr) (mL/min)	**Total Pregabalin Daily Dose (mg/day)[a]**				**Dose Regimen**
≥60	150	300	450	600	b.i.d. or t.i.d.
30–60	75	150	225	300	b.i.d. or t.i.d.
15–30	25–50	75	100–150	150	q.d. or b.i.d.
<15	25	25–50	50–75	75	q.d.

[a] Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose.

t.i.d.= Three divided doses; b.i.d.= Two divided doses; q.d.= Single daily dose.

For patients undergoing haemodialysis, pregabalin daily dose should be adjusted based on renal function. In addition to the daily dose adjustment, a supplemental dose should be given immediately following every 4-hour haemodialysis treatment as mentioned below:

Supplementary Dosage Following Haemodialysis (mg)[b]	
Patients on the 25 mg q.d. regimen	Take one supplemental dose of 25 mg or 50 mg
Patients on the 25–50 mg q.d.regimen	Take one supplemental dose of 50 mg or 75 mg
Patients on the 50–75 mg q.d. regimen	Take one supplemental dose of 75 mg or 100 mg
Patients on the 75 mg q.d. regimen	Take one supplemental dose of 100 mg or 150 mg

[b] Supplementary dose is a single additional dose.

Contraindications

Patients who are hypersensitive to pregabalin or any of the components of this product. Angio-oedema and hypersensitivity reactions have occurred in patients receiving pregabalin therapy.

Warnings and Precautions

Angio-oedema

There have been post-marketing reports of angioedema in patients during initial and chronic treatment with pregabalin. Specific symptoms included swelling of the face, mouth (tongue, lips, and gums), and neck (throat and larynx). There were reports of life-threatening angioedema with respiratory compromise requiring emergency treatment. **NOVA PLUS** should be discontinued immediately in patients with these symptoms.

Caution should be exercised when prescribing **NOVA PLUS** to patients who have had a previous episode of angio-oedema. In addition, patients who are taking other drugs associated with angio-oedema (e.g. angiotensin-converting enzyme inhibitors [ACEinhibitors]) may be at increased risk of developing angio-oedema.

Hypersensitivity

There have been postmarketing reports of hypersensitivity in patients shortly after initiation of treatment with pregabalin. Adverse reactions included skin redness, blisters, hives, rash, dyspnoea, and wheezing. **NOVA PLUS** should be discontinued immediately in patients with these symptoms.

Withdrawal of Anti-Epileptic Drugs

As with all anti-epileptic drugs (AEDs), pregabalin should be withdrawn gradually to minimize the potential of increased seizure frequency in patients with seizure disorders. If **NOVA PLUS** is discontinued, it should be tapered gradually over a minimum of 1 week.

Suicidal Behaviour and Ideation

AEDs, including pregabalin, increase the risk of suicidal thoughts or behaviour in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behaviour, and/or any unusual changes in mood or behaviour.

Anyone considering prescribing pregabalin or any other AED must balance the risk of suicidal thoughts or behaviour with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behaviour. Should suicidal thoughts and behaviour emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behaviour and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behaviour, or the emergence of suicidal thoughts, behaviour, or thoughts about self-harm. Behaviours of concern should be reported immediately to healthcare providers.

Peripheral Oedema

Pregabalin treatment may cause peripheral oedema. In short-term trials of patients without clinically significant heart or peripheral vascular disease, there was no apparent association between peripheral oedema and cardiovascular complications such as hypertension or congestive heart failure. Peripheral oedema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function.

Higher frequencies of weight gain and peripheral oedema were observed in patients taking both pregabalin and a thiazolidinedione antidiabetic agent compared to patients taking either drug alone. As the thiazolidinedione class of antidiabetic drugs can cause weight gain and/or fluid retention, possibly exacerbating or leading to heart failure, care should be taken when co-administering pregabalin and these agents.

Because there are limited data on congestive heart failure patients with New York Heart Association (NYHA) Class III or IV cardiac status**, NOVA PLUS** should be used with caution in these patients.

Dizziness and Somnolence

Pregabalin may cause dizziness and somnolence. Patients should be informed that pregabalin-related dizziness and somnolence may impair their ability to perform tasks such as driving or operating machinery.

In the pregabalin controlled trials, both dizziness and somnolence was experienced more in the pregabalin group compared to placebo. Dizziness and somnolence generally began shortly after the initiation of pregabalin therapy and occurred more frequently at higher doses. Dizziness and somnolence were the adverse reactions most frequently leading to withdrawal.

Weight Gain

Pregabalin treatment may cause weight gain. In pregabalin controlled clinical trials, pregabalin-associated weight gain was related to dose and duration of exposure, but did not appear to be associated with baseline body mass index, gender, or age. Weight gain was not limited to patients with oedema.

Although weight gain was not associated with clinically important changes in blood pressure in short-term controlled studies, the long-term cardiovascular effects of pregabalin-associated weight gain are unknown.

Among diabetes patients, pregabalin was associated with higher weight gain as compared to placebo treated patients. However, the effects of this pregabalin-associated weight gain on glycaemic control have not been systematically assessed. In controlled and longer-term open label clinical trials with diabetes patients, pregabalin treatment did not appear to be associated with loss of glycaemic control (as measured by HbA1c).

Tumourigenic Potential

In clinical studies across various patient populations, comprising 6,396 patient-years of exposure in patients >12 years of age, new or worsening pre-existing tumours were reported in 57 patients. Without knowledge of the background incidence and recurrence in similar populations not treated

with pregabalin, it is impossible to know whether the incidence seen in these cohorts is or is not affected by treatment.

Ophthalmological Effects

In controlled studies, a higher proportion of patients treated with pregabalin reported blurred vision than did patients treated with placebo, which resolved in a majority of cases with continued dosing. Few patients experienced reduction in visual acuity and changes in visual field and fundoscopy. Less than 1% of patients discontinued pregabalin treatment due to vision-related events (primarily, blurred vision).

Although the clinical significance of the ophthalmologic findings is unknown, patients should be informed that if changes in vision occur, they should notify their physician. If visual disturbance persists, further assessment should be considered. More frequent assessment should be considered for patients who are already routinely monitored for ocular conditions.

Creatine Kinase Elevations

Pregabalin treatment was associated with creatine kinase elevations. The relationship between the myopathy events and pregabalin is not completely understood because the cases had documented factors that may have caused or contributed to these events. Patients should be instructed to promptly report unexplained muscle pain, tenderness, or weakness, particularly if these muscle symptoms are accompanied by malaise or fever. **NOVA PLUS** treatment should be discontinued if myopathy is diagnosed or suspected or if markedly elevated creatine kinase levels occur.

Decreased Platelet Count

Pregabalin treatment was associated with a decrease in platelet count. Pregabalin-treated subjects experienced a mean maximal decrease in platelet count of $20 \times 10^3/\mu L$, compared to $11 \times 10^3/\mu L$ in placebo patients. In the overall database of controlled trials, 2% of placebo patients and 3% of pregabalin patients experienced a potentially clinically significant decrease in platelets, defined as 20% below baseline value and $<150 \times 10^3/\mu L$. A single pregabalin treated subject developed severe thrombocytopenia with a platelet count less than $20 \times 10^3/\mu L$. In randomized controlled trials, pregabalin was not associated with an increase in bleeding-related adverse reactions.

PR Interval Prolongation

Pregabalin treatment was associated with PR interval prolongation. In analyses of clinical trial electrocardiogram (ECG) data, the mean PR interval increase was 3–6 msec at pregabalin doses ≥300 mg/day. This mean change difference was not associated with an increased risk of PR increase ≥25% from baseline, an increased percentage of subjects with on-treatment PR >200 msec, or an increased risk of adverse reactions of second or third-degree atrioventricular (AV) block.

Subgroup analyses did not identify an increased risk of PR prolongation in patients with baseline PR prolongation or in patients taking other PR prolonging medications. However, these analyses cannot be considered definitive because of the limited number of patients in these categories.

Diabetes Patients

In accordance with current clinical practice, some diabetes patients who gain weight on pregabalin treatment may need to adjust hypoglycaemic medicinal products.

Congestive Heart Failure

There have been post-marketing reports of congestive heart failure in some patients receiving pregabalin. These reactions are mostly seen in elderly cardiovascular compromised patients during pregabalin treatment for a neuropathic indication. **NOVA PLUS** should be used with caution in these patients. Discontinuation may resolve the reaction.

Reduced Lower Gastrointestinal Tract Function

There are post-marketing reports of events related to reduced lower gastrointestinal tract function (e.g., intestinal obstruction, paralytic ileus, constipation) when pregabalin was co-administered with medications that have the potential to produce constipation, such as opioid analgesics. When **NOVA PLUS** and opioids will be used in combination, measures to prevent constipation may be considered (especially in female patients and the elderly).

Encephalopathy

Cases of encephalopathy have been reported with the use of pregabalin, mostly in patients with underlying conditions that may precipitate encephalopathy.

Abrupt or Rapid Discontinuation

Following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache, anxiety, hyperhidrosis, and diarrhoea. **NOVA PLUS** should be tapered gradually over a minimum of 1 week rather than discontinued abruptly.

Effects on Ability to Drive and Use Machines

Pregabalin may have minor or moderate influence on the ability to drive and use machines. Pregabalin may cause dizziness and somnolence and, therefore, may influence the ability to drive or use machines. Patients are advised not to drive, operate complex machinery or engage in other potentially hazardous activities until it is known whether this medicinal product affects their ability to perform these activities.

Drug Interactions

Since pregabalin is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (<2% of a dose recovered in urine as metabolites), and does not bind to plasma proteins, its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions or protein binding displacement. *In vitro* and *in vivo* studies showed that pregabalin is unlikely to be involved in significant pharmacokinetic drug interactions.

In vitro Studies

Pregabalin, at concentrations that were, in general, 10times those attained in clinical trials, does not inhibit human CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 enzyme systems. *In vitro* drug interaction studies demonstrate that pregabalin does not induce CYP1A2 or CYP3A4 activity. Therefore, an increase in the metabolism of co-administered CYP1A2 substrates (e.g. theophylline, caffeine) or CYP3A4 substrates (e.g. midazolam, testosterone) is not anticipated.

In vivo Studies

The drug interaction studies described in this section were conducted in healthy adults, and across various patient populations.

Gabapentin

Gabapentin pharmacokinetics following single- and multiple-dose administration was unaltered by pregabalin co-administration. The extent of pregabalin absorption was unaffected by gabapentin co-administration, although there was a small reduction in rate of absorption.

Oral Contraceptives

Pregabalin co-administration (200 mg three times a day) had no effect on the steady-state pharmacokinetics of norethindrone and ethinyl oestradiol (1 mg/35 µg, respectively) in healthy subjects.

Lorazepam

Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects had no effect on the rate and extent of lorazepam single-dose pharmacokinetics and single-dose administration of lorazepam (1 mg) had no effect on the steady-state pharmacokinetics of pregabalin.

Oxycodone

Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects had no effect on the rate and extent of oxycodone single-dose pharmacokinetics. Single-dose administration of oxycodone (10 mg) had no effect on the steady-state pharmacokinetics of pregabalin.

Ethanol

Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects had no effect on the rate and extent of ethanol single-dose pharmacokinetics and single-dose administration of ethanol (0.7 g/kg) had no effect on the steady-state pharmacokinetics of pregabalin. Regular consumption of alcohol is an important risk factor for the development and the progression of neuropathic clinical pictures and may therefore also have a negative influence on the success of treatment with this combination. For this reason, it is generally recommended for patients suffering from diabetic neuropathy to avoid the consumption of alcohol as far as possible. This shall also apply to treatment-free intervals.

AEDs

Steady-state trough plasma concentrations of phenytoin, phenobarbital, topiramate, carbamazepine and carbamazepine 10, 11 epoxide, valproic acid, and lamotrigine were not affected by concomitant pregabalin (200 mg three times a day) administration. These drugs have no effect on the pharmacokinetics of pregabalin and pregabalin has no effect on the pharmacokinetics of the mentioned drugs. Tiagabine also had no affect the pharmacokinetics of pregabalin.

Antidiabetic Agents

Concomitant administration of glyburide, insulin or metformin with pregabalin did not affect the pharmacokinetics of pregabalin.

Additive hypoglycaemic effects may occur with concomitant use of antidiabetic agents and alpha-lipoic acid. Close monitoring of blood sugar is recommended when starting with therapy with alpha-

lipoic acid.

Furosemide

Concomitant administration of furosemide with pregabalin did not affect the pharmacokinetics of pregabalin.

Cisplatin

Alpha-lipoic acid antagonizes the action of cisplatin and may result in decreased cisplatin effectiveness

Metal-containing Products

Alpha-lipoic acid readily chemically reacts with metals (metal chelator) and should, therefore, not be administered together with metal containing products (e.g. iron preparations, magnesium preparations and milk products due to their calcium content) because it may neutralize their effect. Some difference in time should be kept while administering this combination with iron and/or magnesium preparations.

Renal Impairment

Cases of renal failure have been reported and in some cases discontinuation of pregabalin did show reversibility of this adverse reaction. Pregabalin dosage adjustment should be considered in cases of renal impairment (refer to **DOSAGE AND ADMINISTRATION>>Patients with Renal Impairment**)

Pregnancy

Pregnancy Category C

Increased incidences of foetal structural abnormalities and other manifestations of developmental toxicity, including lethality, growth retardation and nervous and reproductive system functional impairment, were observed in the offspring of rats and rabbits given pregabalin during pregnancy at doses that produced plasma pregabalin exposures (AUC) ≥5 times human exposure at the maximum recommended dose of 600 mg/day.

There are no adequate and well-controlled studies for the use of pregabalin in pregnant women. No USFDA rating is available for alpha-lipoic acid and mecobalamin. Pregabalin should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Lactation

It is not known if pregabalin is excreted in human milk; it is, however, present in the milk of rats. Because many drugs are excreted in human milk, and because of the potential for tumourigenicity shown for pregabalin in animal studies, a decision should be made whether to discontinue nursing or to discontinue the combination, taking into account the importance of the drug to the mother.

Paediatric Use

Safety and effectiveness of any of the components of this product in paediatric patients have not been established.

Geriatric Use

No overall differences in safety and efficacy were observed between patients≥75 years of age and younger patients. Even though the incidence of adverse events did not increase with age, greater sensitivity of some older individuals cannot be ruled out. Pregabalin is known to be substantially excreted by the kidney, and the risk of toxic reactions to pregabalin may be greater in patients with impaired renal function. Because pregabalin is eliminated primarily by renal excretion, the dose should be adjusted for elderly patients with renal impairment.

Drug Abuse and Dependence

Controlled Substance

Pregabalin is a Schedule V controlled substance.

Pregabalin is not known to be active at receptor sites associated with drugs of abuse. As with any CNS active drug, physicians should carefully evaluate patients for history of drug abuse and observe them for signs of pregabalin misuse or abuse (e.g. development of tolerance, dose escalation, and drug-seeking behaviour).

Abuse

In a study of recreational users (N=15) of sedative/hypnotic drugs, including alcohol, pregabalin (450 mg, single dose) received subjective ratings of “good drug effect”, “high” and “liking” to a degree that was similar to diazepam (30 mg, single dose). In controlled clinical studies in over 5,500 patients, 4% of pregabalin-treated patients and 1% of placebo-treated patients overall reported euphoria as an adverse reaction, though in some patient populations studied, this reporting rate was higher and ranged 1–12%.

Dependence

In clinical studies, following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache or diarrhoea, consistent with physical dependence. In the postmarketing experience, in addition to these reported symptoms there have also been reported cases of anxiety and hyperhidrosis.

Undesirable Effects

Pregabalin

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In all controlled and uncontrolled trials across various patient populations during the premarketing development of pregabalin, more than 10,000 patients have received pregabalin. Approximately 5,000 patients were treated for 6 months or more, over 3,100 patients were treated for 1 year or longer, and over 1,400 patients were treated for at least 2 years.

Adverse Reactions Most Commonly Leading to Discontinuation in All Premarketing Controlled Clinical Studies

In premarketing controlled trials of all populations combined, 14% of patients treated with pregabalin and 7% of patients treated with placebo discontinued prematurely due to adverse reactions. In the pregabalin group, the adverse reactions most frequently leading to discontinuation were dizziness (4%) and somnolence (4%). In the placebo group, 1% of patients withdrew due to dizziness and <1% withdrew due to somnolence. Other adverse reactions that led to discontinuation from controlled trials more frequently in the pregabalin group compared to the placebo group were ataxia, confusion, asthenia, thinking abnormal, blurred vision, in coordination, and peripheral oedema (1% each).

Most Common Adverse Reactions in All Premarketing Controlled Clinical Studies

In premarketing controlled trials of all patient populations combined, dizziness, somnolence, drymouth, oedema, blurred vision, weight gain, and 'thinking abnormal' (primarily difficulty with concentration / attention) were more commonly reported by subjects treated with pregabalin than by subjects treated with placebo(≥5% and twice the rate of that seen in placebo).

Controlled Studies with Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

Adverse Reactions Leading to Discontinuation: In clinical trials in patients with neuropathic pain associated with diabetic peripheral neuropathy,9% of patients treated with pregabalin and 4% of patients treated with placebo discontinued prematurely due to adverse reactions. In the pregabalin group, the most common reasons for discontinuation due to adverse reactions were dizziness (3%) and somnolence (2%).In comparison,<1% of placebo patients withdrew due to dizziness and somnolence. Other reasons for discontinuation from the trials, occurring with greater frequency in the pregabalin group than in the placebo group, were asthenia, confusion, and peripheral oedema. Each of these events led to withdrawal in approximately 1% of patients.

***Most Common Adverse Reactions*:** Table 2 lists all adverse reactions, regardless of causality, occurring in ≥1%of patients with neuropathic pain associated with diabetic neuropathy in the combined pregabalin group for which the incidence was greater in this combined pregabalin group than in the placebo group. A majority of pregabalin-treated patients in clinical studies had adverse reactions with a maximum intensity of 'mild' or 'moderate'.

Table 2: Treatment-emergent Adverse Reaction Incidence in Controlled Trials in Neuropathic Pain Associated with Diabetic Peripheral Neuropathy (Events in At Least 1% of All Pregabalin-Treated Patients and At Least Numerically More in All Pregabalin than In the Placebo Group)

Body System Preferred Term	75 mg/day [N=77] %	150 mg/day [N=212] %	300 mg/day [N=321] %	600 mg/day [N=369] %	All Pregabalin [N=979] %	Placebo [N=459] %
Body as a Whole						
Asthenia	4	2	4	7	5	2
Accidental injury	5	2	2	6	4	3
Back pain	0	2	1	2	2	0
Chest pain	4	1	1	2	2	1
Face oedema	0	1	1	2	1	0
Digestive System						

Body System Preferred Term	75 mg/day [N=77] %	150 mg/day [N=212] %	300 mg/day [N=321] %	600 mg/day [N=369] %	All Pregabalin [N=979] %	Placebo [N=459] %
Dry mouth	3	2	5	7	5	1
Constipation	0	2	4	6	4	2
Flatulence	3	0	2	3	2	1
Metabolic and Nutritional Disorders						
Peripheral oedema	4	6	9	12	9	2
Weight gain	0	4	4	6	4	0
Oedema	0	2	4	2	2	0
Hypoglycaemia	1	3	2	1	2	1
Nervous System						
Dizziness	8	9	23	29	21	5
Somnolence	4	6	13	16	12	3
Neuropathy	9	2	2	5	4	3
Ataxia	6	1	2	4	3	1
Vertigo	1	2	2	4	3	1
Confusion	0	1	2	3	2	1
Euphoria	0	0	3	2	2	0
Incoordination	1	0	2	2	2	0
Thinking abnormal†	1	0	1	3	2	0
Tremor	1	1	1	2	1	0
Abnormal gait	1	0	1	3	1	0
Amnesia	3	1	0	2	1	0
Nervousness	0	1	1	1	1	0
Respiratory System						
Dyspnoea	3	0	2	2	2	1
Special Senses						
Blurry vision‡	3	1	3	6	4	2
Abnormal vision	1	0	1	1	1	0

† Thinking abnormal primarily consists of events related to difficulty with concentration/attention, but also includes events related to cognition and language problems and slowed thinking.

‡ Investigator term; summary level term is amblyopia

Other Adverse Reactions Observed During the Clinical Studies of Pregabalin

Following is a list of treatment-emergent adverse reactions reported by patients treated with pregabalin during all clinical trials. The listing does not include those events already listed in the previous tables or elsewhere in labelling, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once, which did

not have a substantial probability of being acutely life-threatening.

Events are categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse reactions are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1,000 patients; rare reactions are those occurring in fewer than 1/1,000 patients.

Body as a Whole

Frequent**:** Abdominal pain, allergic reaction, fever, increase in weight

Infrequent: Abscess, cellulitis, chills, malaise, neck rigidity, overdose, pelvic pain, photosensitivity reaction

Rare: Anaphylactoid reaction, ascites, granuloma, hangover effect, intentional injury, retroperitoneal fibrosis, shock

Cardiovascular System

Infrequent: Deep thrombophlebitis, congestive heart failure, hypotension, postural hypotension, retinal vascular disorder, syncope,tachycardia, atrioventricular block first degree, sinus bradycardia

Rare: ST depressed, ventricular fibrillation, QT prolongation, sinus tachycardia, sinus arrhythmia

Digestive System

Frequent: Gastroenteritis, increased appetite, vomiting, nausea, constipation, diarrhoea, flatulence, abdominal distension, dry mouth

Infrequent: Cholecystitis, cholelithiasis, colitis, dysphagia, oesophagitis, gastritis, gastrointestinal haemorrhage, melaena, mouth ulceration, pancreatitis, rectal haemorrhage, tongue oedema, gastro-oesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral

Rare: Aphthous stomatitis, oesophageal ulcer, periodontal abscess, ascites, pancreatitis, dysphagia

Haemic and Lymphatic System

Frequent: Ecchymosis

Infrequent: Anaemia, eosinophilia, hypochromic anaemia, leucocytosis, leukopenia, lymphadenopathy, thrombocytopenia, neutropenia

Rare: Myelofibrosis, polycythaemia, prothrombin decreased, purpura, thrombocythaemia

Metabolic and Nutritional Disorders

Infrequent: Anorexia, hypoglycaemia

Rare: Glucose tolerance decreased, urate crystalluria

Musculoskeletal and Connective Tissue Disorders

Frequent: Arthralgia, leg cramps, myalgia, myasthenia, back pain, pain in limb, cervical spasm

Infrequent: Arthrosis, joint swelling, muscle twitching, neck pain, muscle stiffness

Rare: Chondrodystrophy, generalised spasm, rhabdomyolysis

Nervous System and Psychiatric Disorders

Frequent: Anxiety, depersonalisation, hypertonia, hypoesthesia, libido decreased, nystagmus, paraesthesia, sedation, stupor, twitching, dizziness, somnolence, headache, ataxia, coordination abnormal, tremor, dysarthria, amnesia, memory impairment, disturbance in attention, lethargy, euphoric mood, confusion, irritability, disorientation, insomnia, paraesthesia, hypoesthesia, sedation, balance disorder

Infrequent: Abnormal dreams, agitation, apathy, aphasia, circumoral paraesthesia, dysarthria, hallucinations, hostility, hyperalgesia, hyperesthesia, hyperkinesia, hypokinesia, hypotonia, libido increased, myoclonus, neuralgia, stupor, myoclonus, loss of consciousness, psychomotor hyperactivity, dizziness postural, intention tremor, nystagmus, cognitive disorder, mental impairment, speech disorder, hyporeflexia, hyperaesthesia, burning sensation, ageusia, panic attack, restlessness, agitation, depression, depressed mood, elevated mood, aggression, mood swings, depersonalisation, word finding difficulty, syncope, dyskinesia, malaise, hallucination, libido increased

Rare: Addiction, cerebellar syndrome, cogwheel rigidity, coma, delirium, delusions, dysautonomia, dyskinesia, dystonia, encephalopathy, extrapyramidal syndrome, Guillain-Barré syndrome, hypoalgesia, intracranial hypertension, manic reaction, paranoid reaction, peripheral neuritis, personality disorder, psychotic depression, schizophrenic reaction, sleep disorder, torticollis, trismus, convulsions, parosmia, hypokinesia, dysgraphia, disinhibition

Respiratory, Thoracic and Mediastinal Disorders

Infrequent: Dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness

Rare: Apnoea, atelectasis, bronchiolitis, hiccup, laryngismus, lung oedema, lung fibrosis, yawn, pulmonary oedema, throat tightness

Skin and Appendages

Frequent: Pruritus

Infrequent: Alopecia, hyperhidrosis, dry skin, eczema, hirsutism, skin ulcer, urticaria, vesiculobullous rash, pruritis

Rare: Angioedema, exfoliative dermatitis, lichenoid dermatitis, melanosis, nail disorder, petechial rash, purpuric rash, pustular rash, skin atrophy, skin necrosis, skin nodule, Stevens-Johnson syndrome, subcutaneous nodule, cold sweat

Special Senses

Frequent: Conjunctivitis, diplopia, otitis media, tinnitus, vision blurred

Infrequent: Abnormality of accommodation, blepharitis, peripheral vision loss, visual acuity reduced, eye pain, asthenopia, photopsia, lacrimation increased, eye irriation, dry eyes, eye haemorrhage, eye swelling, visual field defect, hyperacusis, photophobia, retinal oedema, taste loss, taste perversion

Rare: Anisocoria, blindness, corneal ulcer, exophthalmos, extraocular palsy, iritis, keratitis, oscillopsia, altered visual depth perception, strabismus, visual brightness, keratoconjunctivitis, miosis, mydriasis, night blindness, ophthalmoplegia, optic atrophy, papilloedema, parosmia, ptosis, uveitis

Urogenital System and Breast Disorders

Frequent: Anorgasmia, impotence, urinary frequency, urinary incontinence

Infrequent: Abnormal ejaculation, albuminuria, amenorrhoea, dysmenorrhoea, dysuria, haematuria, kidney calculus, leucorrhoea, menorrhagia, metrorrhagia, nephritis, oliguria, urinary retention, urine abnormality, breast pain

Rare: Acute kidney failure, balanitis, bladder neoplasm, cervicitis, dyspareunia, epididymitis, female lactation, glomerulitis, ovarian disorder, pyelonephritis, breast discharge, breast enlargement, gynaecomastia

Infections and Infestations

Frequent: Nasopharyngitis

Vascular Disorders

Infrequent: Hypotension, hypertension, hot flushes, flushing, peripheral coldness

General Disorders and Administration Site Conditions

Frequent: Oedema, peripheral oedema, gait abnormal, fall, feeling drunk, feeling abnormal, fatigue

Infrequent: Generalized oedema, face oedema, chest tightness, pain, pyrexia, thirst

Investigations

Infrequent: Blood creatine phosphokinase increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood glucose increased, platelet count decreased, blood creatinine increased, blood potassium decreased, weight decreased

Withdrawal Symptoms

After discontinuation of short-term and long-term treatment with pregabalin withdrawal symptoms have been observed in some patients. The following reactions have been mentioned: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, convulsions, nervousness, depression, pain, hyperhidrosis and dizziness, suggestive of physical dependence. The patient should be informed about this at the start of the treatment. Concerning discontinuation of long-term treatment of pregabalin, data suggest that the incidence and severity of withdrawal symptoms may be dose related.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of pregabalin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Nervous System Disorders: Headache

- Gastrointestinal Disorders: Nausea, diarrhoea
- Reproductive System and Breast Disorders: Gynaecomastia, breast enlargement

In addition, there are postmarketing reports of events related to reduced lower gastrointestinal tract function (e.g. intestinal obstruction, paralytic ileus, constipation) when pregabalin was co-administered with medications that have the potential to produce constipation, such as opioid analgesics. There are also postmarketing reports of respiratory failure and coma in patients taking pregabalin and other central nervous system depressant medications.

Mecobalamin

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.

Alpha-lipoic Acid

Evaluation of the side effects of alpha-lipoic acid is based on the following frequency information:

Very common: more than 1 of 10 treated patients

Common: less than 1 of 10, however more than 1 of 100 treated patients

Uncommon: less than 1 of 100, however more than 1 of 1,000 treated patients

Rare: less than 1 of 1,000, however more than 1 of 10,000 treated patients

Very rare: less than 1 of 10,000 treated patients, including isolated reports

Gastrointestinal Tract

Common: Vertigo

Very rare: Vomiting, pain in the stomach and/or in the intestine and diarrhoea.

Hypersensitivity Reactions

Very rare: Allergic reactions such as skin rash, nettle rash (urticaria) and itching.

Nervous System

Common: Dizziness

Very rare: Change or disturbance of taste sensation

General Disorders

Very rare: Due to enhanced glucose utilization, the blood sugar level may drop. In this relation,

hypoglycaemic symptoms accompanied by dizziness, sweating, headache and blurred vision were described.

Overdosage

Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans

There is limited experience with overdose of pregabalin. The highest reported accidental overdose of pregabalin during the clinical development programme was 8,000 mg and there were no notable clinical consequences.

Treatment or Management of Overdose

There is no specific antidote for overdose with pregabalin. If indicated, elimination of unabsorbed drug may be attempted by emesis or gastric lavage; usual precautions should be observed to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient.

Although haemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment. Standard haemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours).

Mecobalamin has excellent tolerability and no known toxicity. At higher doses of alpha-lipoic acid, gastrointestinal symptoms, including abdominal pain, nausea, and vomiting, as well as diarrhoea, and anaphylactic reactions, including laryngospasm, were reported. Also, allergic reactions affecting the skin, including rashes, hives and itching, have been reported with high doses of alpha-lipoic acid.

Incompatibility

None

Shelf-Life

2 years

Storage and Handling Instructions

Store in a cool, dry and dark place. Protect from light.

Packaging Information

NOVA PLUS 75 Capsules: Blister pack of 10 capsules

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