NOVA Capsules (Pregabalin)

Composition

NOVA 75

Each capsule contains Pregabalin .....75 mg

Dosage Form

Capsules

Pharmacology

Pharmacodynamics

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. However, in cultured neurons, prolonged application of pregabalin increases the density of GABA transporter protein and increases the rate of functional GABA transport.

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 antinociceptive and antiseizure effects in animal models. *In vitro*, pregabalin reduces the calcium dependent release of several neurotransmitters, possibly by modulation of calcium channel function.

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.

Pharmacokinetics

Pregabalin is well absorbed after oral administration, is eliminated largely by renal excretion and has an elimination half-life of about 6 hours.

Absorption

Following oral administration of pregabalin capsules under fasting conditions, peak plasma concentrations occur within 1.5 hours. Pregabalin oral bioavailability is ≥ 90% and is independent of dose. Following single - (25 to 300 mg) and multiple- dose (75 to 900 mg/day) administration, maximum plasma concentrations (C_{max}) and area under the plasma concentration-time curve (AUC) values increase linearly. Following repeated administration, steady state is achieved within 24 to 48

hours.

The rate of pregabalin absorption is decreased when given with food, resulting in a decrease in C_{max} of approximately 25% to 30% and an increase in T_{max} to approximately 3 hours. However, administration of pregabalin with food has no clinically relevant effect on the total absorption of pregabalin. Therefore, pregabalin can be taken with or without food.

Distribution

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.

Metabolism

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.

Excretion

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).

Special populations

Geriatrics

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

Gender

Population pharmacokinetic analyses of the clinical studies showed that the relationship between daily dose and pregabalin drug exposure is similar between genders.

Renal impairment and haemodialysis

Pregabalin clearance is nearly proportional to creatinine clearance (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.

Paediatric Pharmacokinetics

Pharmacokinetics of pregabalin has not been adequately studied in paediatric patients.

Indication

NOVA is indicated for the treatment of:

Management of neuropathic pain associated with diabetic peripheral neuropathy

Management of postherpetic neuralgia

Adjunctive therapy for adult patients with partial onset seizures

Management of fibromyalgia

Management of neuropathic pain associated with spinal cord injury

Dosage and Administration

NOVA is given orally with or without food

Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

The maximum recommended dose of 100 mg three times a day (300 mg/day) in patients with creatinine clearance of at least 60 mL/min. Begin dosing at 50 mg three times a day (150 mg/day). The dose may be increased to 300 mg/day within 1 week based on efficacy and tolerability. 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 reactions, treatment with doses above 300 mg/day is not recommended

Postherpetic Neuralgia

The recommended dose of pregabalin is 75 to 150 mg two times a day, or 50 to 100 mg three times a day (150 to 300 mg/day) in patients with creatinine clearance of at least 60 mL/min. Begin dosing at 75 mg two times a day, or 50 mg three times a day (150 mg/day). The dose may be increased to 300 mg/day within 1 week based on efficacy and tolerability.

Adjunctive Therapy for Adult Patients with Partial Onset Seizures

Pregabalin at doses of 150 to 600 mg/day has been shown to be effective as adjunctive therapy in the treatment of partial onset seizures in adults.

Management of Fibromyalgia

The recommended dose of pregabalin for fibromyalgia is 300 to 450 mg/day. Begin dosing at 75 mg two times a day (150 mg/day). The dose may be increased to 150 mg two times a day (300 mg/day) within 1 week based on efficacy and tolerability.

Neuropathic Pain Associated with Spinal Cord Injury

The recommended dose range of pregabalin for the treatment of neuropathic pain associated with spinal cord injury is 150 to 600 mg/day. The recommended starting dose is 75 mg two times a day (150 mg/day). The dose may be increased to 150 mg two times a day (300 mg/day) within 1 week

based on efficacy and tolerability.

Discontinuation of pregabalin

If **NOVA** has to be discontinued, it is recommended this should be done gradually over a minimum of 1 week.

Patients with renal impairment

In view of dose-dependent adverse events 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 on creatinine clearance (CLcr), as indicated in Table 1, determined by the following formula:

$$CL_{cr}\ (ml/min) = \frac{[140 - age(years)] \times weight\ (kg)}{72 \times serum\ creatinine\ (mg/dl)} \times (0.85\ for\ female\ patients)$$

Table 1: Pregabalin Dosage Adjustment Based on Renal Function

Creatinine Clearance (CLcr) (mL/min)	**Total Pregabalin Daily Dose (mg/day)***				**Dose Regimen**
≥ 60	150	300	450	600	BID or TID
30-60	75	150	225	300	BID or TID
15-30	25-50	75	100-150	150	QD or BID
<15	25	25-50	50-75	75	QD
Supplementary dosage following hemodialysis (mg)†					
Patients on the 25 mg QD regimen: take one supplemental dose of 25 mg or 50 mg Patients on the 25–50 mg QD regimen: take one supplemental dose of 50 mg or 75 mg Patients on the 50–75 mg QD regimen: take one supplemental dose of 75 mg or 100 mg Patients on the 75 mg QD regimen: take one supplemental dose of 100 mg or 150 mg					

TID = Three divided doses; BID = Two divided doses; QD = Single daily dose.

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

† Supplementary dose is a single additional dose.

For patients undergoing hemodialysis, 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 hemodialysis treatment as mentioned in Table 1.

Contraindications

Patients who are hypersensitive to pregabalin or any of the components of this product.

Warnings and Precautions

General

Angioedema

There have been postmarketing 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. Pregabalin should be discontinued immediately in patients with these symptoms.

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

Hypersensitivity

There have been postmarketing reports of hypersensitivity in patients shortly after initiation of treatment with pregabalin. Undesirable effects included skin redness, blisters, hives, rash, dyspnea, and wheezing. Pregabalin should be discontinued immediately in patients with these symptoms.

Suicidal behavior and ideation

Antiepileptic drugs (AEDs), including pregabalin, increase the risk of suicidal thoughts or behavior 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 behavior, and/or any unusual changes in mood or behavior.

Anyone considering prescribing pregabalin or any other AED must balance the risk of suicidal thoughts or behavior 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 behavior. Should suicidal thoughts and behavior 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 behavior 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 behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

Tumorigenic Potential

In standard preclinical *in vivo* lifetime carcinogenicity studies of pregabalin, an unexpectedly high incidence of hemangiosarcoma was identified in two different strains of mice. The clinical significance of this finding is unknown. Clinical experience during pregabalin's premarketing development provides no direct means to assess its potential for inducing tumors in humans.

In clinical studies across various patient populations, comprising 6396 patient-years of exposure in patients >12 years of age, new or worsening-preexisting tumors 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.

Treatment of central neuropathic pain due to spinal cord injury

In the treatment of central neuropathic pain due to spinal cord injury the incidence of adverse reactions in general, central nervous system adverse reactions and especially somnolence was increased. This may be attributed to an additive effect due to concomitant medicinal products (e.g. anti-spasticity agents) needed for this condition. This should be considered when prescribing pregabalin in this condition.

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, dizziness was experienced by 30% of pregabalin - treated patients compared to 8% of placebo-treated patients; somnolence was experienced by 23% of pregabalin - treated patients compared to 8% of placebo-treated patients. Dizziness and somnolence generally began shortly after the initiation of pregabalin therapy and occurred more frequently at higher doses. Dizziness and somnolence were the undesirable effects most frequently leading to withdrawal from controlled studies. In pregabalin - treated patients reporting these undesirable effects in short-term, controlled studies, dizziness persisted until the last dose in 30% and somnolence persisted until the last dose in 42% of patients.

Ophthalmological Effects

In controlled studies, a higher proportion of patients treated with pregabalin reported ophthalmological effects like blurred vision, reduction in visual acuity and changes in visual field and fundoscopy.

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.

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 pregabalin and opioids will be used in combination, measures to prevent constipation may be considered (especially in female patients and elderly).

Abuse potential

Cases of abuse have been reported. Caution should be exercised in patients with a history of substance abuse and the patient should be monitored for symptoms of pregabalin abuse.

Encephalopathy

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

Lactose intolerance

Pregabalin contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Withdrawal symptoms

After discontinuation of short-term and long-term treatment with pregabalin withdrawal symptoms have been observed in some patients. The following events have been mentioned: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, nervousness, depression, pain, convulsion, hyperhidrosis and dizziness. The patient should be informed about this at the start of the treatment.

Convulsions, including status epilepticus and grand mal convulsions, may occur during pregabalin use or shortly after discontinuing pregabalin.

Concerning discontinuation of long-term treatment of pregabalin there are no data of the incidence and severity of withdrawal symptoms in relation to duration of use and dose of pregabalin.

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 BMI, gender, or age. Weight gain was not limited to patients with edema.

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 diabetic patients, pregabalin was associated with higher weight gain as compared to placebo treated patients. However, the effects of this pregabalin-associated weight gain on glycemic control have not been systematically assessed. In controlled and longer-term open label clinical trials with diabetic patients, pregabalin treatment did not appear to be associated with loss of glycemic control (as measured by HbA_{1c}).

Dermatopathy

Diabetic patients should be instructed to pay particular attention to skin integrity while being treated with pregabalin. Some animals treated with pregabalin developed skin ulcerations, although no increased incidence of skin lesions associated with pregabalin was observed in clinical trials.

Male fertility

Men being treated with pregabalin whoa plan to father a child should be informed of the potential risk of male-mediated teratogenicity. In preclinical studies in rats, pregabalin was associated with an increased risk of male-mediated teratogenicity. The clinical significance of this finding is uncertain.

Peripheral Edema

Pregabalin treatment may cause edema, primarily described as peripheral edema. In short- term

trials of patients without clinically significant heart or peripheral vascular disease, there was no apparent association between peripheral edema and cardiovascular complications such as hypertension or congestive heart failure. Peripheral edema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function.

Higher frequencies of weight gain and peripheral edema 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**,** pregabalin should be used with caution in these patients.

Creatine Kinase Elevations

Pregabalin treatment was associated with creatine kinase elevations as compared to placebo in controlled clinical trials. The relationship between these 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. Pregabalin 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 undesirable effects.

PR Interval Prolongation

Pregabalin treatment was associated with PR interval prolongation. In analyses of clinical trial 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 undesirable effects of second or third degree 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.

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 behavior).

Drug Interactions

Pregabalin, at concentrations that were, in general, 10-times 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 coadministered CYP1A2 substrates (e.g. theophylline, caffeine) or CYP 3A4 substrates (e.g. midazolam, testosterone) is not anticipated.

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

Gabapentin

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

Oral Contraceptive

Pregabalin coadministration (200 mg three times a day) had no effect on the steady-state pharmacokinetics of norethindrone and ethinyl estradiol (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.

Antiepileptic Drugs

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.

As with all AEDs, pregabalin should be withdrawn gradually to minimize the potential of increased in patients with seizure disorders. If pregabalin is discontinued this should be done gradually over a minimum of 1 week.

Oral hypoglycaemics

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

Furosemide

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

CNS Depressants

Patients who require concomitant treatment with CNS depressants such as opiates or benzodiazepines should be informed that they may experience additive CNS side effects, such as somnolence.

Alcohol

Patients should be told to avoid consuming alcohol while taking pregabalin, as pregabalin may potentiate the impairment of motor skills and sedating effects of alcohol.

Renal impairment

Pregabalin dosage adjustment should be considered in cases of renal impairment. (Refer Dosage and Administration, Patients with renal impairment)

Pregnancy

Pregnancy Category C

Increased incidences of fetal 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 in pregnant women. 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 tumorigenicity shown for pregabalin in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Paediatric use

Safety and effectiveness in paediatric patients have not been established.

Geriatric use

No overall differences in safety and efficacy were observed between these patients 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.

Undesirable Effects

The most common side effects events seen with pregabalin treatment are dizziness, somnolence, headache, ataxia, asthenia, dry mouth, constipation, edema, blurred vision, weight gain, and “thinking abnormal” (primarily difficulty with concentration/attention).

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 5000 patients were treated for 6 months or more, over 3100 patients were treated for 1 year or longer, and over 1400 patients were treated for at least 2 years.

Undesirable Effects 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 undesirable effects. In the pregabalin treatment group, the undesirable effects most frequently leading to discontinuation were dizziness (4%) and somnolence (3%). In the placebo group, 1% of patients withdrew due to dizziness and <1% withdrew due to somnolence. Other undesirable effects 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, incoordination, and peripheral edema (1% each).

Controlled Studies with Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

Undesirable Effects 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 undesirable effects. In the pregabalin treatment group, the most common reasons for discontinuation due to undesirable effects 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 edema. Each of these events led to withdrawal in approximately 1% of patients.

Most Common Undesirable Effects

Table 2 lists all undesirable effects, 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 undesirable effects 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 PGB* [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 edema	0	1	1	2	1	0
Digestive system						
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 edema	4	6	9	12	9	2
Weight gain	0	4	4	6	4	0
Edema	0	2	4	2	2	0
Hypoglycemia	1	3	2	1	2	1
Nervous system						
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						
Dyspnea	3	0	2	2	2	1
Special senses						
Blurry vision[‡]	3	1	3	6	4	2
Abnormal vision	1	0	1	1	1	0

* PGB: pregabalin

[†] 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

Controlled Studies in Postherpetic Neuralgia

Undesirable Effects Leading to Discontinuation

In clinical trials in patients with postherpetic neuralgia, 14% of patients treated with pregabalin and 7% of patients treated with placebo discontinued prematurely due to undesirable effects. In the pregabalin treatment group, the most common reasons for discontinuation due to undesirable effects were dizziness (4%) and somnolence (3%). In comparison, less than 1% of placebo patients withdrew due to dizziness and somnolence. Other reasons for discontinuation from the trials, occurring in greater frequency in the pregabalin group than in the placebo group, were confusion (2%), as well as peripheral edema, asthenia, ataxia, and abnormal gait (1% each).

Most Common Undesirable Effects

Table 3 lists all undesirable effects, regardless of causality, occurring in ≥ 1% of patients with neuropathic pain associated with postherpetic neuralgia in the combined pregabalin group for which the incidence was greater in this combined pregabalin group than in the placebo group. In addition, an event is included, even if the incidence in the all pregabalin group is not greater than in the placebo group, if the incidence of the event in the 600 mg/day group is more than twice that in the placebo group. A majority of pregabalin-treated patients in clinical studies had undesirable effects with a maximum intensity of "mild" or "moderate”. Overall, 12.4% of all pregabalin-treated patients and 9.0% of all placebo-treated patients had at least one severe event while 8% of pregabalin-treated patients and 4.3% of placebo-treated patients had at least one severe treatment-related adverse

event.

Table 3:Treatment-emergent adverse reaction incidence in controlled trials in Neuropathic Pain Associated with Postherpetic Neuralgia (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/d [N=84] %	150 mg/d [N=302] %	300 mg/d [N=312] %	600 mg/d [N=154] %	All PGB* [N=852] %	Placebo [N=398] %
Body as a whole						
Infection	14	8	6	3	7	4
Headache	5	9	5	8	7	5
Pain	5	4	5	5	5	4
Accidental injury	4	3	3	5	3	2
Flu syndrome	1	2	2	1	2	1
Face edema	0	2	1	3	2	1
Digestive system						
Dry mouth	7	7	6	15	8	3
Constipation	4	5	5	5	5	2
Flatulence	2	1	2	3	2	1
Vomiting	1	1	3	3	2	1
Metabolic and nutritional disorders						
Peripheral edema	0	8	16	16	12	4
Weight gain	1	2	5	7	4	0
Edema	0	1	2	6	2	1
Musculoskeletal system						
Myasthenia	1	1	1	1	1	0
Nervous system						
Dizziness	11	18s	31	37	26	9
Somnolence	8	12	18	25	16	5
Ataxia	1	2	5	9	5	1
Abnormal gait	0	2	4	8	4	1
Confusion	1	2	3	7	3	0

Thinking abnormal[†]	0	2	1	6	2	2
Incoordination	2	2	1	3	2	0
Amnesia	0	1	1	4	2	0
Speech disorder	0	0	1	3	1	0
Respiratory system						
Bronchitis	0	1	1	3	1	1
Special senses						
Blurry vision[‡]	1	5	5	9	5	3
Diplopia	0	2	2	4	2	0
Abnormal vision	0	1	2	5	2	0
Eye Disorder	0	1	1	2	1	0
Urogenital System						
Urinary Incontinence	0	1	1	2	1	0

* PGB: pregabalin

[†] 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

Controlled Studies with Fibromyalgia

Undesirable Effects Leading to Discontinuation

In clinical trials of patients with fibromyalgia, 19% of patients treated with pregabalin (150–600 mg/day) and 10% of patients treated with placebo discontinued prematurely due to undesirable effects. In the pregabalin treatment group, the most common reasons for discontinuation due to undesirable effects were dizziness (6%) and somnolence (3%). In comparison, <1% of placebo-treated patients withdrew due to dizziness and somnolence. Other reasons for discontinuation from the trials, occurring with greater frequency in the pregabalin treatment group than in the placebo treatment group, were fatigue, headache, balance disorder, and weight increased. Each of these undesirable effects led to withdrawal in approximately 1% of patients.

Most Common Undesirable Effects

Table 4 lists all undesirable effects, regardless of causality, occurring in ≥2% of patients with fibromyalgia in the ‘all pregabalin’ treatment group for which the incidence was greater than in the placebo treatment group. A majority of pregabalin-treated patients in clinical studies experienced undesirable effects with a maximum intensity of "mild" or "moderate".

Table 4:Treatment-emergent adverse reaction incidence in controlled trials in

Fibromyalgia (Events in at least 2% of all pregabalin -treated patients and occurring more frequently in the all pregabalin-group than in the placebo treatment group)

System organ Class -Preferred term	150 mg/d [N=132] %	300 mg/d [N=502] %	450 mg/d [N=505] %	600 mg/d [N=378] %	All PGB* [N=1517] %	Placebo [N=505] %
Ear and Labyrinth Disorders						
Vertigo	2	2	2	1	2	0
Eye Disorders						
Vision blurred	8	7	7	12	8	1
Gastrointestinal Disorders						
Dry mouth	7	6	9	9	8	2
Constipation	4	4	7	10	7	2
Vomiting	2	3	3	2	3	2
Flatulence	1	1	2	2	2	1
Abdominal distention	2	2	2	2	2	1
General Disorders and Administrative Site Conditions						
Fatigue	5	7	6	8	7	4
Edema peripheral	5	5	6	9	6	2
Chest pain	2	1	1	2	2	1
Feeling abnormal	1	3	2	2	2	0
Edema	1	2	1	2	2	1
Feeling drunk	1	2	1	2	2	0

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 program was 8000 mg, and there were no notable clinical consequences. In clinical studies, some patients took as much as 2400 mg/day. The types of adverse events experienced by patients exposed to higher doses (≥900 mg) were not clinically

different from those of patients administered recommended doses of pregabalin.

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 hemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours).

Packaging Information

NOVA 75: Blister pack of 10 capsules

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