NEURALIC

Capsules

Composition

Neuralic 75
Each Capsule contains Pregabalin 75 mg
Neuralic 150
Each Capsule contains Pregabalin 150 mg
Neuralic 300
Each Capsule contains Pregabalin 300 mg

Action

Mechanism of Action
Pregabalin binds with high affinity to the alpha2-delta site (an auxiliary subunit of voltage-gated calcium channels) in central nervous system tissues. Although the mechanism of action of Pregabalin has not been fully elucidated, results with genetically modified mice and with compounds structurally related to Pregabalin (such as gabapentin) suggest that binding to the alpha2-delta subunit may be involved in Pregabalin's anti-nociceptive and antiseizure 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 alpha2-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.

While Pregabalin is a structural derivative of the inhibitory neurotransmitter gammaaminobutyric acid (GABA), it does not bind directly to GABAA, GABAB, or benzodiazepine receptors, does not augment GABAA 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 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 and Distribution
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 (Cmax) and area under the plasma concentration-time curve (AUC) values increase linearly. Following repeated administration, steady state is achieved within 24 to 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 Cmax of approximately 25% to 30% and an increase in Tmax 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.

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.

Metabolism and Elimination
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 (Senantiomer) 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).

Pharmacokinetics in Special Populations
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).
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 Hemodialysis
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 hemodialysis. Following a 4-hour hemodialysis treatment, plasma Pregabalin concentrations are reduced by approximately 50%. For patients on hemodialysis, dosing must be modified.

Elderly
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.

Pediatric Pharmacokinetics
Pharmacokinetics of Pregabalin has not been adequately studied in pediatric patients.

Indications
- 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

Contraindications
Pregabalin is contraindicated in patients with known hypersensitivity to Pregabalin or any of its components. Angioedema and hypersensitivity reactions have occurred in patients receiving Pregabalin therapy.

Adverse Reactions
The most commonly reported adverse reactions were dizziness and somnolence. Adverse reactions were usually mild to moderate in intensity. In all controlled studies, the discontinuation rate due to adverse reactions was 12% for patients receiving Pregabalin and 5% for patients receiving placebo. The most common adverse reactions resulting in discontinuation from Pregabalin treatment groups were dizziness and somnolence.

In the table below all adverse reactions, which occurred at an incidence greater than placebo and in more than one patient, are listed by class and frequency (very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The adverse reactions listed may also be associated with the underlying disease and / or concomitant medicinal products.

In the treatment of central neuropathic pain due to spinal cord injury the incidence of adverse reactions in general, CNS adverse reactions and especially somnolence was increased.

Additional reactions reported from post-marketing experience are included in italics in the list below.

System Organ Class	**Adverse drug reactions**
Infections and infestations	
Common	Nasopharyngitis
Blood and lymphatic system disorders	
Uncommon	Neutropenia
Immune system disorders	
Uncommon	*Hypersensitivity*
Rare	*Angioedema, allergic reaction*
Metabolism and nutrition disorders	
Common	Appetite increased
Uncommon	Anorexia, hypoglycaemia
Psychiatric disorders	
Common	Euphoric mood, confusion, irritability, disorientation, insomnia, libido decreased
Uncommon	Hallucination, panic attack, restlessness, agitation, depression, depressed mood, elevated mood, *aggression*, mood swings, depersonalisation, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy
Rare	Disinhibition
Nervous system disorders	
Very Common	Dizziness, somnolence, headache
Common	Ataxia, coordination abnormal, tremor, dysarthria, amnesia, memory impairment, disturbance in attention, paraesthesia, hypoaesthesia, sedation, balance disorder, lethargy
Uncommon	Syncope, stupor, myoclonus, *loss of consciousness*, psychomotor hyperactivity, dyskinesia, dizziness postural, intention tremor, nystagmus, cognitive disorder, *mental impairment*, speech disorder, hyporeflexia, hyperaesthesia, burning sensation, ageusia, *malaise*
Rare	*Convulsions*, parosmia, hypokinesia, dysgraphia

Eye disorders	
Common	Vision blurred, diplopia
Uncommon	Peripheral vision loss, visual disturbance, eye swelling, visual field defect, visual acuity reduced, eye pain, asthenopia, photopsia, dry eye, lacrimation increased, eye irritation
Rare	*Vision loss, keratitis*, oscillopsia, altered visual depth perception, mydriasis, strabismus, visual brightness
Ear and labyrinth disorders	
Common	Vertigo
Uncommon	Hyperacusis
Cardiac disorders	
Uncommon	Tachycardia, atrioventricular block first degree, sinus bradycardia, *congestive heart failure*
Rare	*QT prolongation*, sinus tachycardia, sinus arrhythmia
Vascular disorders	
Uncommon	Hypotension, hypertension, hot flushes, flushing, peripheral coldness
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness
Rare	*Pulmonary oedema*, throat tightness,
Gastrointestinal disorders	
Common	Vomiting, *nausea*, constipation, *diarrhoea*, flatulence, abdominal distension, dry mouth
Uncommon	Gastrooesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral
Rare	Ascites, pancreatitis, *swollen tongue*, dysphagia
Skin and subcutaneous tissue disorders	
Uncommon	Rash papular, urticaria, hyperhidrosis, *pruritus*
Rare	*Stevens Johnson syndrome,* cold sweat
Musculoskeletal and connective tissue disorders	
Common	Muscle cramp, arthralgia, back pain, pain in limb, cervical spasm
Uncommon	Joint swelling, myalgia, muscle twitching, neck pain, muscle stiffness
Rare	Rhabdomyolysis
Renal and urinary disorders	
Uncommon	Urinary incontinence, dysuria
Rare	Renal failure, oliguria, *urinary retention*
Reproductive system and breast disorders	

Common	Erectile dysfunction
Uncommon	Sexual dysfunction, ejaculation delayed, dysmenorrhoea, breast pain
Rare	Amenorrhoea, breast discharge, breast enlargement, *gynaecomastia*
General disorders and administration site conditions	
Common	Oedema peripheral, oedema, gait abnormal, fall, feeling drunk, feeling abnormal, fatigue
Uncommon	Generalised oedema, *face oedema*, chest tightness, pain, pyrexia, thirst, chills, asthenia
Investigations	
Common	Weight increased
Uncommon	Blood creatine phosphokinase increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood glucose increased, platelet count decreased, blood creatinine increased, blood potassium decreased, weight decreased
Rare	White blood cell count decreased

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. 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.

Warnings and Precautions

Diabetic patients

In accordance with current clinical practice, some diabetic patients who gain weight on Pregabalin treatment may need to adjust hypoglycemic medicinal products.

Hypersensitivity reactions

There have been reports in the post marketing experience of hypersensitivity reactions, including cases of angioedema. Pregabalin should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper airway swelling occur.

Dizziness, somnolence, loss of consciousness, confusion, and mental impairment

Pregabalin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in the elderly population. There have also been post-marketing reports of loss of consciousness, confusion and mental impairment. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medicinal product.

Vision-related effects

In controlled trials, 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. In the clinical studies where ophthalmologic testing was conducted, the incidence of visual acuity reduction and visual field changes was greater in Pregabalin-treated patients than in placebo-treated patients; the incidence of fundoscopic changes was greater in placebo-treated patients.

In the post-marketing experience, visual adverse reactions have also been reported, including loss of vision, visual blurring or other changes of visual acuity, many of which were transient. Discontinuation of Pregabalin may result in resolution or improvement of these visual symptoms.

Renal failure
Cases of renal failure have been reported and in some cases discontinuation of Pregabalin did show reversibility of this adverse reaction.

Withdrawal of concomitant antiepileptic medicinal products
There are insufficient data for the withdrawal of concomitant antiepileptic medicinal products, once seizure control with Pregabalin in the add-on situation has been reached, in order to reach monotherapy on Pregabalin.

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, data suggest that the incidence and severity of withdrawal symptoms may be dose-related.

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. Pregabalin should be used with caution in these patients. Discontinuation of Pregabalin may resolve the reaction.

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.

Suicidal ideation and behavior
Suicidal ideation and behavior have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomized placebo controlled studies of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behavior. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for Pregabalin.

Therefore patients should be monitored for signs of suicidal ideation and behaviors and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behavior emerge.

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.

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 (MRD) of 600 mg/day.

There are no adequate and well-controlled studies in pregnant women. Use Pregabalin during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery
The effects of Pregabalin on labor and delivery in pregnant women are unknown. In the prenatal-postnatal study in rats, Pregabalin prolonged gestation and induced dystocia at exposures ≥ 50 times the mean human exposure (AUC (0–24) of 123 µg•hr/mL) at the maximum recommended clinical dose of 600 mg/day.

Nursing Mothers
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, decide whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
The safety and efficacy of Pregabalin in pediatric patients have not been established.
In studies in which Pregabalin (50 to 500 mg/kg) was orally administered to young rats from early in the postnatal period (Postnatal Day 7) through sexual maturity, neurobehavioral abnormalities (deficits in learning and memory, altered locomotor activity, decreased auditory startle responding and habituation) and reproductive impairment (delayed sexual maturation and decreased fertility in males and females) were observed at doses ≥ 50 mg/kg. The neurobehavioral changes of acoustic startle persisted at ≥ 250 mg/kg and locomotor activity and water maze performance at ≥ 500 mg/kg in animals tested after cessation of dosing and, thus, were considered to represent long-term effects. The low effect dose for developmental neurotoxicity and reproductive impairment in juvenile rats (50 mg/kg) was associated with a plasma Pregabalin exposure (AUC) approximately equal to human exposure at the maximum recommended dose of 600 mg/day. A no-effect dose was not established.

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

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, adjust the dose for elderly patients with renal impairment

Drug Interactions
In Vitro Studies
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.

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

Gabapentin
The pharmacokinetic interactions of Pregabalin and gabapentin were investigated in 12 healthy subjects following concomitant single-dose administration of 100-mg Pregabalin and 300-mg gabapentin and in 18 healthy subjects following concomitant multiple-dose administration of 200-mg Pregabalin every 8 hours and 400-mg gabapentin every 8 hours. Gabapentin pharmacokinetics following single-and multiple-dose administration was 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.

Phenytoin, carbamazepine, valproic acid, and lamotrigine
Steady-state trough plasma concentrations of phenytoin, carbamazepine and carbamazepine 10, 11 epoxide, valproic acid, and lamotrigine were not affected by concomitant Pregabalin (200 mg three times a day) administration.

Population pharmacokinetic analyses in patients treated with Pregabalin and various concomitant medications suggest the following:

Therapeutic class	Specific concomitant drug studied
Concomitant drug has no effect on the pharmacokinetics of Pregabalin	
Hypoglycemics	Glyburide, insulin, metformin
Diuretics	Furosemide
Antiepileptic Drugs	Tiagabine
Concomitant drug has no effect on the pharmacokinetics of Pregabalin and Pregabalin has no effect on the pharmacokinetics of concomitant drug	
Antiepileptic Drugs	Carbamazepine, lamotrigine, phenobarbital, phenytoin, topiramate, valproic acid

Dosage and Administration
Pregabalin is given orally with or without food.

When discontinuing Pregabalin, taper gradually over a minimum of 1 week.

Neuropathic Pain Associated With Diabetic Peripheral Neuropathy
The maximum recommended dose of Pregabalin is 300 mg/day in patients with creatinine clearance of at least 60 mL/min. Begin dosing at 75 mg tow times a day (150 mg/day). The dose may be increased to 300 mg/day within 1 week based on efficacy and tolerability. Because Pregabalin is eliminated primarily by renal excretion, adjust the dose in 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 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 (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 (150 mg/day). The dose may be increased to 300 mg/day within 1 week based on efficacy and tolerability. Because Pregabalin is eliminated primarily by renal excretion, adjust the dose in patients with reduced renal function.

Patients who do not experience sufficient pain relief following 2 to 4 weeks of treatment with 300 mg/day, and who are able to tolerate Pregabalin, may be treated with up to 300 mg two times a day (600 mg/day). In view of the dose-dependent adverse reactions and the higher rate of treatment discontinuation due to adverse reactions, reserve dosing above 300 mg/day for those patients who have on-going pain and are tolerating 300 mg daily.

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. Both the efficacy and adverse event profiles of Pregabalin have been shown to be dose-related. Administer the total daily dose in two or three divided doses. In general, it is recommended that patients be started on a total daily dose no greater than 150 mg/day (75 mg two times a day). Based on individual patient response and tolerability, the dose may be increased to a maximum dose of 600 mg/day.

Because Pregabalin is eliminated primarily by renal excretion, adjust the dose in patients with reduced renal function. The effect of dose escalation rate on the tolerability of Pregabalin has not been formally studied.

The efficacy of add-on Pregabalin in patients taking gabapentin has not been evaluated in controlled trials. Consequently, dosing recommendations for the use of Pregabalin with gabapentin cannot be offered.

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. Patients who do not experience sufficient benefit with 300 mg/day may be further increased to 450 mg/day. Although Pregabalin was also studied at 600 mg/day, there is no evidence that this dose confers additional benefit and this dose was less well tolerated. In view of the dose-dependent adverse reactions, treatment with doses above 450 mg/day is not recommended. Because Pregabalin is eliminated primarily by renal excretion, adjust the dose in patients with reduced renal function.

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. Patients who do not experience sufficient pain relief after 2 to 3

weeks of treatment with 150 mg two times a day and who tolerate Pregabalin may be treated with up to 300 mg two times a day. Because Pregabalin is eliminated primarily by renal excretion, adjust the dose in patients with reduced renal function.

Patients with Renal Impairment
In view of dose-dependent adverse reactions and since Pregabalin is eliminated primarily by renal excretion, adjust the dose in patients with reduced renal function. Base the dose adjustment in patients with renal impairment on creatinine clearance (CLcr), as indicated in Table. To use this dosing table, an estimate of the patient's CLcr in mL/min is needed. CLcr in mL/min may be estimated from serum creatinine (mg/dL) determination using the Cockcroft and Gault equation:

Males: $\frac{\text{(weight in kg) x (140 – age)}}{\text{(72) x serum creatinine (mg/100 mL)}}$

Females (0.85) x (above value)

Next, refer to the Dosage and Administration section to determine the recommended total daily dose based on indication, for a patient with normal renal function (CLcr ≥ 60 mL/min). Then refer to the Table below to determine the corresponding renal adjusted dose.

(For example: A patient initiating Pregabalin therapy for postherpetic neuralgia with normal renal function (CLcr ≥ 60 mL/min), receives a total daily dose of 150 mg/day Pregabalin. Therefore, a renal impaired patient with a CLcr of 50 mL/min would receive a total daily dose of 75 mg/day Pregabalin administered in two or three divided doses.)

For patients undergoing hemodialysis, adjust the Pregabalin daily dose based on renal function. In addition to the daily dose adjustment, administer a supplemental dose immediately following every 4-hour hemodialysis treatment (see Table).

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

Use in Hepatic Impairment
No dosage adjustment is required for patients with hepatic impairment

Use in Children and Adolescents (<18 years)
The safety and effectiveness of Pregabalin has not been established in patients below the age of 18 years, with either epilepsy or neuropathic pain.

Use in the Elderly (>65 years)
No dosage adjustment is necessary for elderly patients unless their renal function is compromised.

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.

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; observe usual precautions 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. Contact a Certified Poison Control Center for up to-date information on the management of overdose with Pregabalin.

Although hemodialysis 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).

Storage Instructions
Store at. 25°C. Protect from moisture.

Presentation
Neuralic 75, 150, 300
Box of 14 capsules