NERGAB

(Pregabalin 50mg, 75mg, 100mg or 150mg Capsules)

For oral use only

COMPOSITION

NERGAB CAPSULE 50mg:
Each capsule contains Pregabalin……50mg

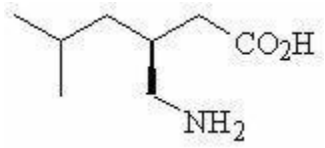
NERGAB CAPSULE 75mg:
Each capsule contains Pregabalin……75mg

NERGAB CAPSULE 100mg:
Each capsule contains Pregabalin……100mg

NERGAB CAPSULE 150mg:
Each capsule contains Pregabalin……150mg

DESCRIPTION

Pregabalin is described chemically as (*S*)-3-(aminomethyl)-5-methylhexanoic acid. The molecular formula is $C_8H_{17}NO_2$ and the molecular weight is 159.23. The chemical structure of pregabalin is:



Pregabalin is a white to off-white, crystalline solid with a pK_{a1} of 4.2 and a pK_{a2} of 10.6. It is freely soluble in water and both basic and acidic aqueous solutions. The log of the partition coefficient (n-octanol/0.05M phosphate buffer) at pH 7.4 is – 1.35.

NERGAB (pregabalin) Capsules are administered orally and are supplied as imprinted hard-shell capsules containing 50, 75, 100, and 150 mg of pregabalin.

CLINICAL PHARMACOLOGY

Mechanism of Action

Nergab (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.

While pregabalin is a structural derivative of the inhibitory neurotransmitter gammaaminobutyric acid (GABA), it 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 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. 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.

Pregabalin does not bind to plasma proteins. 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. 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.

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.

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

Pediatrics: Pharmacokinetics of pregabalin have not been adequately studied in pediatric patients.

INDICATIONS

NERGAB (Pregabalin) is indicated for:
- 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

NERGAB is given orally with or without food.

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

Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

The maximum recommended dose of NERGAB is 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. 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 NERGAB 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. 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 (NERGAB), may be treated with up to 300 mg two times a day, or 200 mg three 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 with NERGAB on a total daily dose no greater than 150 mg/day (75 mg two times a day, or 50 mg three 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 eliminated primarily by renal excretion, adjust the dose in patients with reduced renal function.

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

Management of Fibromyalgia

The recommended dose of NERGAB 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 225 mg two times a day (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 NERGAB 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 (NERGAB) 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 below:

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
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.

CONTRAINDICATIONS

NERGAB (Pregabalin) is contraindicated in patients with known hypersensitivity to pregabalin or any of its components.

WARNINGS AND PRECAUTIONS:

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. Discontinue NERGAB (pregabalin) immediately in patients with these symptoms.

Exercise caution when prescribing NERGAB (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. Adverse reactions included skin redness, blisters, hives, rash, dyspnea, and wheezing. Discontinue NERGAB (pregabalin) immediately in patients with these symptoms

Withdrawal of Antiepileptic Drugs (AEDs)
As with all AEDs, NERGAB (pregabalin) should be withdrawn gradually to minimize the potential of increased seizure frequency in patients with seizure disorders. If NERGAB (pregabalin) is discontinued, taper the drug gradually over a minimum of 1 week. .

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. Monitor patients treated with any AED for any indication for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

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.

Dizziness and Somnolence
Pregabalin causes 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 29% of pregabalin treated patients compared to 9% of placebo-treated patients; somnolence was experienced by 22% 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 adverse events most frequently leading to withdrawal (4% each) from controlled studies. In pregabalin-treated patients reporting these adverse events in short-term, controlled studies, dizziness persisted until the last dose in 31% and somnolence persisted until the last dose in 46% of patients.

Ophthalmological Effects
In controlled studies, a higher proportion of patients treated with pregabalin reported blurred vision (6%) than did patients treated with placebo (2%), which resolved in a majority of cases with continued dosing. Less than 1% of patients discontinued pregabalin treatment due to vision-related events (primarily blurred vision). Prospectively planned ophthalmologic testing, including visual acuity testing, formal visual field testing and dilated fundoscopic examination, was performed in over 3600 patients.

Abrupt or Rapid Discontinuation
Following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache, and diarrhea. Pregabalin should be tapered gradually over a minimum of 1 week rather than discontinued abruptly.

Weight Gain
Pregabalin treatment caused weight gain. In pregabalin controlled clinical trials of up to 13 weeks, a gain of 7% or more over baseline weight was observed in 8% of pregabalin treated patients and 2% of placebo-treated patients. Few patients treated with pregabalin (0.2%) withdrew from controlled trials due to weight gain. 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.

Peripheral Edema
Pregabalin treatment caused 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.

Creatine Kinase Elevations
Pregabalin treatment was associated with creatine kinase elevations. Mean changes in creatine kinase from baseline to the maximum value were 60 U/L for pregabalin-treated patients and 28 U/L for the placebo patients. In all controlled trials across multiple patient populations, 2% of patients on pregabalin and 1% of placebo patients had a value of creatine kinase at least three times the upper limit of normal. Three pregabalin treated subjects had events reported as rhabdomyolysis in premarketing clinical trials.

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 × 103/µL, compared to 11 × 103/µL 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 × 103/µL. A single pregabalin treated subject developed severe thrombocytopenia with a platelet count less than 20 × 103/ µL. 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 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 AV block.

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. Specifically, there are no pharmacokinetic interactions between pregabalin and the following antiepileptic drugs: carbamazepine, valproic acid, lamotrigine, phenytoin, phenobarbital, and topiramate. Important pharmacokinetic interactions would also not be expected to occur between pregabalin and commonly used antiepileptic drugs.

Pharmacodynamics

Multiple oral doses of pregabalin were co-administered with oxycodone, lorazepam, or ethanol. Although no pharmacokinetic interactions were seen, additive effects on cognitive and gross motor functioning were seen when pregabalin was co-administered with these drugs. No clinically important effects on respiration were seen

USE IN SPECIFIC POPULATIONS 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 NERGAB during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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, 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.

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.

Geriatric Use
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

ADVERSE REACTIONS
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.

Body as a Whole
- *Frequent:* Abdominal pain, Allergic reaction, Fever,
- *Infrequent:* Abscess, Cellulitis, Chills, Malaise, Neck rigidity, Overdose, Pelvic pain, Photosensitivity reaction
- *Rare:* Anaphylactoid reaction, Ascites, Granuloma, Hangover effect, Intentional injury, Retroperitoneal fibrosis, Shock, Suicide attempts

Cardiovascular System
–*Infrequent:* Deep thrombophlebitis, Heart failure, Postural hypotension, Syncope;
–*Rare:* ST depression, Ventricular fibrillation

Digestive System
- *Frequent*: Gastroenteritis, Increased appetite;
- *Infrequent:* Cholecystitis, Cholelithiasis, Colitis, Dysphagia, Esophagitis, Gastritis, Gastrointestinal hemorrhage, Melena, Mouth ulceration, Pancreatitis, Rectal hemorrhage, Tongue edema;
- *Rare:* Aphthous stomatitis, Esophageal ulcer

Hemic and Lymphatic System
- *Frequent:* Ecchymosis;
- *Infrequent:* Anemia, Eosinophilia, Leukocytosis, Leukopenia, Thrombocytopenia;
- *Rare:* Myelofibrosis, Polycythemia, Prothrombin decreased, Purpura,

Metabolic and Nutritional Disorders
– *Rare:* Glucose tolerance decreased, Urate crystalluria

Musculoskeletal System
- *Frequent*: Arthralgia, Leg cramps, Myalgia, Myasthenia;
- *Infrequent:* Arthrosis;
- *Rare:* Generalized spasm

Nervous System
- *Frequent:* Anxiety, Depersonalization, Hypertonia, Hypersthesia, Libido decreased, Nystagmus, Paresthesia, Stupor, Twitching;
- *Infrequent:* Abnormal dreams, Agitation, Apathy, Aphasia, Circumoral paresthesia, Dysarthria, Hallucinations, Hostility, Hyperalgesia, Hyperesthesia, Hyperkinesia,
- *Rare:* Addiction, Cerebellar syndrome, Cogwheel rigidity, Coma, Delirium, Delusions, Dysautonomia, Dyskinesia, Dystonia, Extrapyramidal syndrome

Skin and Appendages
- *Frequent:* Pruritus,
- *Infrequent:* Alopecia, Dry skin, Eczema, Hirsutism, Skin ulcer, Urticaria,
- *Rare:* Angioedema, Exfoliative dermatitis, Lichenoid dermatitis

Special Senses
- *Frequent:* Conjunctivitis, Diplopia, Otitis media, Tinnitus;
- *Infrequent:* Abnormality of accommodation, Blepharitis, Dry eyes, Eye hemorrhage, Hyperacusis, Photophobia, Retinal edema, Taste loss, Taste perversion;

– *Rare:* Anisocoria, Blindness, Corneal ulcer, Exophthalmos, Extraocular palsy

Urogenital System
– *Frequent*: Anorgasmia, Impotence, Urinary frequency, Urinary incontinence,
– *Infrequent*: Abnormal ejaculation, Albuminuria, Amenorrhea, Dysmenorrhea, Dysuria, Hematuria, Kidney calculus, Leukorrhea, Menorrhagia, Metrorrhagia, Nephritis, Oliguria,
– *Rare*: Acute kidney failure, Balanitis, Bladder Neoplasm, Cervicitis, Dyspareunia, Epididymitis, Female lactation, Glomerulitis

OVERDOSAGE

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.

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.

PRESENTATION

– **50mg capsules:** Nergab 50mg capsules in the blister packs of 2 x 7's
– **75mg capsules:** Nergab 75mg capsules in the blister packs of 2 x 7's.
– **100mg capsules:** Nergab 100mg capsules in the blister packs of 2 x 7's.
– **150mg capsules:** Nergab 150mg capsules in the blister packs of 2 x 7's.

INSTRUCTIONS

– To be sold on the prescription of a registered medical practitioner only.
– Store below 30º C.
– Protect from sunlight and moisture.
– Keep out of reach of children.

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CIR-NGB-0415

PAK-NGB-C-042015