PREGABALIN

LIGABA

75 mg Capsule
150 mg Capsule
Antiepileptic

FORMULATION:

Each hard gelatin capsule contains:

Pregabalin	75mg
Pregabalin	150mg

DOSAGE AND ADMINISTRATION:

The maximum recommended dose range is 150-600 mg per day.

Given orally with or without food. When discontinuing, taper gradually over a minimum of 1 week. Because it is eliminated primarily by renal excretion, adjust the dose in patients with reduced renal function.

Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

The maximum recommended dose 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.

Postherpetic Neuralgia

The recommended dose 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.

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, 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

A dose of 150 to 600 mg/day has been shown to be effective as adjunctive therapy in the treatment of partial onset seizures in adults. 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, 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.

Management of Fibromyalgia

The recommended dose 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). In view of the dose-dependent adverse reactions, treatment with doses above 450 mg/day is not recommended.

Neuropathic Pain Associated with Spinal Cord Injury

The recommended dose range 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, may be treated with up to 300 mg two times a day.

Dosage Adjustment with Renal Impairment

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.

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

CLINICAL PHARMACOLOGY:

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.

Pharmacodynamics:

Pharmacotherapeutic group: Antiepileptics, other antiepileptics.

CLINICAL EXPERIENCE:

Neuropathic pain:

Efficacy has been shown in trials in diabetic neuropathy, post herpetic neuralgia and spinal cord injury. Efficacy has not been studied in other models of neuropathic pain.

Pregabalin has been studied in 10 controlled clinical trials of up to 13 weeks with twice a day dosing (BID) and up to 8 weeks with three times as day (TID) dosing. Overall, the safety and efficacy profiles for BID and TID dosing regimens were similar.

In clinical trials up to 12 weeks for both peripheral and central neuropathic pain, a reduction in pain was seen by week 1 and was maintained throughout the treatment period.

In controlled clinical trials in peripheral neuropathic pain 35% of the pregabalin treated patients and 18% of the patients on placebo had a 50% improvement in pain score. For patients not experiencing somnolence, such an improvement was observed in 33% of patients treated with pregabalin and 18% of patients on placebo. For patients who experienced somnolence the responder rates were 48% on pregabalin and 16% on placebo.

In the controlled clinical trial in central neuropathic pain 22% of the Pregabalin treated patients and 7% of the patients on placebo had a 50% improvement in pain score.

Epilepsy:

Pregabalin has been studied in 3 controlled clinical trials of 12 week duration with either twice a day dosing (BID) or three times a day (TID) dosing. Overall, the safety and efficacy profiles for BID and TID dosing regimens were similar. A reduction in seizure frequency was observed by Week 1.

Generalised Anxiety Disorder:

Pregabalin has been studied in 6 controlled trials of 4-6 week duration, an elderly study of 8 week duration and a long-term relapse prevention study with a double blind relapse prevention phase of 6 months duration.

Relief of the symptoms of GAD as reflected by the Hamilton Anxiety Rating Scale (HAM-A) was observed by Week 1.

In controlled clinical trials (4-8 week duration) 52% of the pregabalin treated patients and 38% of the patients on placebo had at least a 50% improvement in HAM-A total score from baseline endpoint.

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. Ophthalmologic testing (including visual acuity testing, formal visual field testing and dilated fundoscopic examination) was conducted in over 3600 patients within controlled clinical trials. In these patients, visual acuity was reduced in 6.5% of patients treated with pregabalin, and 4.8% of placebo-treated patients. Visual field changes were detected in 12.4% of pregabalin-treated, and 11.7% of placebo-treated patients. Funduscopic changes were observed in 1.7% of pregabalin-treated and 2.1% of placebo-treated patients.

PHARMACOKINETICS:

Pregabalin steady-state pharmacokinetics are similar in healthy volunteers, patients with epilepsy receiving anti-epileptic drugs and patients with chronic pain.

Absorption

Pregabalin is rapidly absorbed when administered in the fasted state, with peak plasma concentrations occurring within 1 hour following both single and multiple dose administration. 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} by approximately 25-30% and a delay in t_{max} to approximately 2.5 hours. However, administration of pregabalin with food has no clinically significant effect on the extent of pregabalin absorption.

Distribution

In preclinical studies, pregabalin has been shown to cross the blood brain barrier in mice, rats and monkeys. Pregabalin has been shown to cross the placenta in rats and is present in the milk of lactating rats. In humans, the apparent volume of distribution of pregabalin following oral administration is approximately 0.56 l/kg. Pregabalin is not bound to plasma proteins.

Biotransformation

Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabelled pregabalin, approximately 98% of the radioactivity recovered in the urine was 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, there was no indication of racemization of pregabalin S-enantiomer to the R-enantiomer.

Elimination

Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. Pregabalin mean elimination half-life is 6.3 hours. Pregabalin plasma clearance and renal clearance are directly proportional to creatinine clearance. Dose adjustment in patients with reduced renal function or undergoing hemodialysis is necessary.

Linearity/non-linearity

Pregabalin pharmacokinetics are linear over the recommended daily dose range. Inter-subject pharmacokinetic variability for pregabalin is low (<20%)

PHARMACOKINETICS IN SPECIAL PATIENT GROUPS

Gender:

Clinical trials indicate that gender does not have a clinically significant influence on the plasma concentrations of pregabalin.

Renal Impairment:

Pregabalin clearance is directly proportional to creatinine clearance. In addition, pregabalin is effectively removed from plasma by hemodialysis (following a 4 hour hemodialysis treatment plasma pregabalin concentrations are reduced by approximately 50%). Because renal elimination is the major elimination pathway, dose reduction in patients with renal impairment and dose supplementation following hemodialysis is necessary.

Hepatic Impairment:

No specific pharmacokinetic studies were carried out in patients with impaired liver function. Since pregabalin does not undergo significant metabolism and is excreted predominantly as unchanged drug in the urine, impaired liver function would not be expected to significantly alter pregabalin plasma concentrations.

Elderly (over 65 years of age):

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

Preclinical safety data:

In conventional safety pharmacology studies in animals, pregabalin was well-tolerated at clinically relevant doses. In repeated dose toxicity studies in rats and monkeys CNS effects were observed, including hypoactivity, hyperactivity and ataxia. An increased incidence of retinal atrophy commonly observed in aged albino rats was seen after long term exposure to pregabalin at exposures ≥ 5 times the mean human exposure at the maximum recommended clinical dose.

Pregabalin was not teratogenic in mice, rats or rabbits. Fetal toxicity in rats and rabbits occurred only at exposures sufficiently above human exposure. In prenatal/postnatal toxicity studies, pregabalin induced offspring developmental toxicity in rats at exposures >2 times the maximum recommended human exposure.

Adverse effects on fertility in male and female rats were only observed at exposures sufficiently in excess of therapeutic exposure. Adverse effects on male reproductive organs and sperm parameters were reversible and occurred only at exposures sufficiently in excess of therapeutic exposure or were associated with spontaneous degenerative processes in male reproductive organs in the rat. Therefore the effects were considered of little or no clinical relevance.

Pregabalin is not genotoxic based on results of a battery of in vitro and in vivo tests.

Two-year carcinogenicity studies with pregabalin were conducted in rats and mice. No tumors were observed in rats at exposures up to 24 times the mean human exposure at the maximum recommended clinical dose of 600 mg/day. In mice, no increased incidence of tumors was found at exposures similar to the mean human exposure, but an increased incidence of hemangiosarcoma was observed at higher exposures. The non-genotoxic mechanism of pregabalin-induced tumor formation in mice involves platelet changes and associated endothelial cell proliferation. These platelet changes were not present in rats or in humans based on short term and limited long term clinical data. There is no evidence to

suggest an associated risk to humans.
In juvenile rats the types of toxicity do not differ qualitatively from those observed in adult rats. However, juvenile rats are more sensitive. At therapeutic exposures, there was evidence of CNS clinical signs of hyperactivity and bruxism and some changes in growth (transient body weight gain suppression). Effects on the estrus cycle were observed at 5-fold the human therapeutic exposure. Reduced acoustic startle response was observed in juvenile rats 1-2 weeks after exposure at >2 times the human therapeutic exposure. Nine weeks after exposure, this effect was no longer observable.

SIDE EFFECTS:
The most common side effects of Pregabalin are:

- Dizziness
- Blurry vision
- Weight gain
- Sleepiness
- Trouble concentrating
- Swelling of hands and feet
- Dry mouth

WARNINGS AND PRECAUTIONS:

Angioedema
There have been postmarketing reports of angioedema in patients during initial and chronic treatment. 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 immediately in patients with these symptoms. Exercise caution when prescribing 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.

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 postmarketing 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.

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.

Suicidal Ideation and Behavior
Suicidal ideation and behavior have been reported in patients 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 the risk is not known and the available data do not exclude the possibility of an increased risk for pregabalin.

Peripheral Edema
Treatment may cause 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.
As the thiazolidinedione class of antidiabetic drugs can cause weight gain and/or fluid retention, possibly exacerbating or leading to heart failure, exercise caution when co-administering with these agents.
Because there are limited data on congestive heart failure patients with New York Heart Association (NYHA) Class III or IV cardiac status, exercise caution when using in these patients.

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.

Weight Gain
Treatment may cause weight gain. It was related to dose and duration of exposure, but did not appear to be associated with baseline BMI, gender, or age.

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, diarrhea, 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.

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 were greater in pregabalin-treated patients than in placebo-treated patients; the incidence of funduscopic 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.

Creatine Kinase Elevations
Treatment was associated with creatine kinase elevations. Three treated subjects had events reported as rhabdomyolysis in premarketing clinical trials. Instruct patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if these muscle symptoms are accompanied by malaise or fever. Discontinue treatment if myopathy is diagnosed or suspected or if markedly elevated creatine kinase levels occur.

Decreased Platelet Count
Treatment was associated with a decrease in platelet count. In randomized controlled trials, drug was not associated with an increase in bleeding-related adverse reactions.

PR Interval Prolongation
Treatment was associated with PR interval prolongation.

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

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.

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

ADVERSE REACTIONS:

- BODY AS A WHOLE: Infection, headache, pain, accidental injury and face edema.
- DIGESTIVE SYSTEM: Dry mouth, constipation, flatulence and vomiting.
- METABOLIC AND NUTRITIONAL DISORDERS: Peripheral edema, weight gain and edema and hypoglycemia.
- NERVOUS SYSTEM: Dizziness, somnolence, ataxia, abnormal gait, confusion, incoordination, amnesia and speech disorder.
- RESPIRATORY SYSTEM: Bronchitis
- SPECIAL SENSE: Blurry vision, diplopia, abnormal vision and eye disorder.
- UROGENITAL SYSTEM: Urinary incontinence.
- REPRODUCTIVE SYSTEM AND BREAST DISORDERS: Gynecomastia and breast enlargement.

DRUG INTERACTIONS:
Since it 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 it 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 this drug and commonly used antiepileptic drugs.

Pharmacodynamics
Multiple oral doses 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 co-administered with these drugs. No clinically important effects on respiration were seen.

SPECIAL POPULATIONS:

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

Breast-feeding
It is not known if pregabalin is excreted in the breast milk of humans; however, it is present in the milk of rats. Therefore, breast-feeding is not recommended during treatment with pregabalin.

Pediatric Use
The safety and efficacy of pregabalin in pediatric patients have not been established.

Fertility
There are no clinical data on the effects of pregabalin on female fertility.
In a clinical trial to assess the effect of pregabalin on sperm motility, healthy male subjects were exposed to pregabalin at a dose of 600 mg/day. After 3 months of treatment, there were no effects on sperm motility.

DRUG ABUSE AND DEPENDENCE:

Controlled Substance
Pregabalin is a Schedule V controlled substance. It is not known to be active at receptor sites associated with drugs of abuse. As with any CNS active drug, carefully evaluate patients for history of drug abuse and observe them for signs of misuse or abuse (e.g., development of tolerance, dose escalation, drug-seeking behavior).

Abuse
In controlled clinical studies in over 5500 patients, 4 % of drug-treated patients and 1 % of placebo-treated patients overall reported euphoria as an adverse reaction, though in some patient populations studied, this reporting rate was higher and ranged from 1 to 12%.

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

OVERDOSAGE AND TREATMENT:
In overdoses up to 15 g, no unexpected adverse reactions were reported.
In the post-marketing experience, the most commonly reported adverse reactions observed when pregabalin was taken in overdose included somnolence, confusional state, agitation, and restlessness.

Treatment or Management of Overdose
There is no specific antidote for overdose with this drug. 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. 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 CONDITION:

- Store at temperatures not exceeding 30°C.
- Protect from light and moisture.
- Keep out of reach of children.

AVAILABILITY:
Box of 30 capsules

CAUTION:
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

B31368-01

Manufactured by : **MSN LABORATORIES PVT. LTD.** (Formulations Division)
Plot No 42, Anrich Industrial Estate,
Bollaram, Sangareddy District – 502 325, Telangana, INDIA.

For : **MEGA LIFESCIENCES (AUSTRALIA) PTY LTD**
Victoria 3810, Australia.

MEGA
We care

Imported & Distributed by: **METRO DRUG, INC.**
Mañalac Avenue, Bagumbayan, Taguig City, Philippines

I-L80D-MPS-00-01