SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Prebaxe 50 capsules

Prebaxe 75 capsules

Prebaxe 150 capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Prebaxe 50 mg hard capsules

Each hard capsule contains 50 mg pregabalin.

Prebaxe 75 mg hard capsules

Each hard capsule contains 75 mg pregabalin.

Prebaxe 150 mg hard capsules

Each hard capsule contains 150 mg pregabalin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules

Prebaxe 50 mg hard capsules

White to off white powder filled in size ‘3’ hard gelatin white opaque and white opaque capsule linear printed in black ink with 'Cipla 50 mg' on the cap and '678'on the body.

Prebaxe 75 mg hard capsules

White to off white powder filled in size ‘4’ hard gelatin orange opaque and white opaque capsule linear printed in black ink with 'Cipla 75 mg' on the cap and ‘679’ on the body.

Prebaxe 150 mg hard capsules

White to off white powder filled in size ‘2’ hard gelatin white opaque and white opaque capsule linear printed in black ink with 'Cipla 150 mg' on the cap and ‘682’ on the body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prebaxe capsules are indicated for:

- Management of neuropathic pain associated with diabatic peripheral neuropathy
- Management of postherpetic neuralgia

- Adjunctive therapy for the trearment of partial- onset seizures in patients 17 years old age and older.
- Management of fibromyalgia
- Management of neuopathic pain associated with spinal cord injury

4.2 Posology and method of administration

Posology

Neuropathic pain associated with diabetic peripheral neuropathy in adults

The maximum recommended dose of pregabalin 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.

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 (see section 4.8).

Postherpetic neuralgia in adults
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.

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, 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 (see section 4.8).

Adjunctive therapy for partial-onset seizures in patients 17 years of age and older

The recommended dosage for adults patients 17 years of age and older are included in table 1. Administer the total daily dosage orally in two or three divided doses as indicated in table 1. Based on clinical response and tolerability, dosage may be increased, approximately weekly.

Table 1. Recommended dosage for adults patients 17 years and older

Age and body weight	Recommended initial dosage	Recommended maximum dosage	Frequency of administration
Adults (17 years and older)	150 mg/day	600 mg/day	2 or 3 divided doses

Both the efficacy and adverse event profiles of pregabalin have been shown to be dose-related.

The effect of dose escalation rate on the tolerability of pregabalin have not been formally studied.

The efficacy of adjunctive 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 in adults

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 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 (see section 4.8).

Neuropathic pain associated with spinal cord injury in adults

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 (see section 4.8).

Renal impairment

In view of dose-dependent adverse reactions and since pregabalin is eliminated primarily by renal excretion, adjust the dose in adult patients with reduced renal function. The use of pregabalin in pediatric patients with compromised renal function has not been studied.

Base the dose adjustment in patients with renal impairment on creatinine clearance (CLcr), as indicated in Table 2. 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:

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

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 greater than or equal to 60 mL/min). Then refer to table 2 to determine the corresponding renal adjusted dose.

(For example: A patient initiating pregabalin therapy for postherpetic neuralgia with normal renal function (CLcr greater than or equal to 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 2).

Table 2. Pregabalin dosage adjustment based on renal function

Creatinine clearance (CLcr) (mL/min)	**Total pregabalin daily dose (mg/day)***				**Dose regimen**
Greater than or equal to 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
Less than 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

TIO=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.

Hepatic impairment

No dose adjustment is required for patients with hepatic impairment.

Pediatric papulation

The safety and efficacy of pregabalin in children below the age of 12 years and in adolescents (12-17 years of age) have not been established.

Elderly

Elderly patients may require a dose reduction or pregabalin due to a decreased renal function.

Method of administration

Prebaxe is for oral use only.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the exipients listed in section 6.1.

Angioedema and hypersensitivity reactions have occurred in patients receiving pregabalin therapy (see section 4.4)

4.4 Special warnings and precautions for use

Angioedema

There have been postmarketing reports of angioedema in patients during initial and chronic treatment with pregabalin capsules. 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 pregabalin capsules immediately in patients with these symptoms.

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

Suicidal behavior and ideation

Antiepileptic drugs (AEDs], including pregabalin capsules, 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.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted relative risk 1.8, 95% Cl:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed.

Table 3 Shows absolute and relative risk by indication for all evaluated AEDs.

Table 3 Risk by indication for Antiepileptic drugs in the pooled analysis

Indication	Placebo patients with events per 1000 patients	Drug patients with events per 1000 patients	Relative risk: incidence of events/ incidence in placebo patients	Risk difference: additional drug patients with events per 1000 patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing pregabalin capsules 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.

Respiratory depression

There is evidence from case reports, human studies, and animal studies associating pregabalin with serious, l1fe-lhreatening, or fatal respiratory depression when co-administered with central nervous system (CNS) depressants, including opioids, or in the setting of underlying respiratory impairment. When the decision is made to co-prescribe pregabalin with another CNS depressant, particularly an opioid, or to prescribe pregabalin to patients with underlying respiratory impairment, monitor patients for symptoms of respiratory depression and sedation, and consider initiating pregabalin at a low dose The management of respiratory depression may include close observation, supportive

measures, and reduction or withdrawal of CNS depressants (Including pregabalin).

There is more limited evidence from case reports, animal studies, and human studies associating pregabalin with serious respiratory depression, without co-administered CNS depressants or without underlying respiratory impairment.

Dizziness and somnolence

Pregabalin capsules may cause dizziness and somnolence. Inform patients that pregabalin capsules-related dizziness and somnolence may impair their ability to perform tasks such as driving or operating machinery.

In the pregabalin controlled trials in adult patients. 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 adverse reactions most frequently leading to withdrawal (4% each) from controlled studies. In pregabalin-treated patients reporting these adverse reactions in short-term, controlled studies, dizziness persisted until the last dose in 30% and somnolence persisted until the last dose in 42% of patients (see section 4.5).

In the pregabalin controlled trials in pediatric patients 4 to less than 17 years of age and 1 month to less than 4 years of age for the treatment of partial-onset seizures, somnolence was reported in 21% and 15% of pregabalin-treated patients compared to 14% and 9% of placebo-treated patients, respectively, and occurred more frequently at higher doses. For patients 1 month to less than 4 years of age, somnolence includes related terms lethargy, sluggishness, and hypersomnia.

Increase risk of adverse reaction with abrupt or rapid discontinuation

As with all antiepileptic drugs (AEDs), withdraw pregabalin gradually to minimize the potential of increased seizure frequency in patients with seizure disorders.

Following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache, anxiety, hyperhidrosis, and Diarrhea.

If pregabalin is discontinued, taper the drug gradually over a minimum of 1 week rather than discontinue the drug abruptly.

Peripheral edema

Pregabalin 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. Peripheral edema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function.

In controlled clinical trials in adult patients, the incidence of peripheral edema was 6% in the pregabalin group compared with 2% In the placebo group. In controlled clinical trials, 0.5% of pregabalin patients and 0.2% placebo patients withdrew due to peripheral edema.

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. The majority of patients using thiazolidinedione antidiabetic agents in the overall safety database were participants in studies of pain associated with diabetic peripheral neuropathy. In this population, peripheral edema was reported in 3% (2/60) of patients who were using thiazolidinedione antidiabetic agents only, 8% (69/859) of patients who were treated with pregabalin only, and 19% (23/120) of patients who were on both pregabalin and thiazolidinedione antidiabetic agents. Similarly, weight gain

was reported in 0% (0/60) of patients on thiazolidinediones only; 4% (35/859) of patients on pregabalin only; and 7.5% (9/120) of patients on both drugs.

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 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, exercise caution when using pregabalin in these patients

Weight Gain

Pregabalin treatment may cause weight gain. In pregabalin controlled clinical trials in adult patients of up to 14 weeks, a gain of 7% or more over baseline weight was observed in 9% of pregabalin -treated patients and 2% o1 placebo-treated patients. Few patients treated with pregabalin (0.3%) withdraw 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.

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-treated patients gained an average of 1.6 kg {range: -16 to 16 kg), compared to an average 0.3 kg (range: -10 to 9 kg) weight gain in placebo patients. In a cohort of 333 diabetic patients who received pregabalin capsules for at least 2 years, the average weight gain was 5.2kg.

While the effects of pregabalin-associated weight gain on glycaemic 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}).

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 capsules 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 greater than 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.

Ophthalmological effects

In controlled studies in adult patients, a higher proportion of patients treated with pregabalin reported blurred vision (7%) 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 funduscopic examination, was performed in over 3600 patients. In these patients, visual acuity was reduced in 7% of patients treated with pregabalin, and 5% of placebo-treated patients. Visual field changes were detected in 13% of pregabalin-treated, and 12% of placebo-treated

patients. Funduscopic changes were observed in 2% of pregabalin-treated and 2% of placebo-treated patients

Although the clinical significance of the ophthalmologic findings is unknown, inform patients to notify their physician if changes in vision occur. If visual disturbance persists, consider further assessment. Consider more frequent assessment for patients who are already routinely monitored for ocular conditions.

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 in adult patients across multiple patient populations, 1.5% of patients on pregabalin and 0.7% 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. The relationship between these myopathy events and pregabalin are not completely understood because the cases had documented factors that may have caused or contributed to these events. Instruct patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if these muscle symptoms are accompanied by malaise or fever. Discontinue treatment with pregabalin 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 x 10^3/µL, compared to 11 x 10^3/µL in placebo patients. In the overall database of controlled trials in adult patients, 2% of placebo patients and 3% of pregabalin patients experienced a potentially clinically significant decrease in platelets, defined as 20% below baseline value and less than 150 x 10^3/µL. A single pregabalin-treated subject developed severe thrombocytopenia with a platelet count less than 20 x 10^3/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 in adult patients, the mean PR interval increase was 3-6 msec at pregabalin doses greater than or equal to 300 mg/day. This mean change difference was not associated with an increased risk of PR increase greater than or equal to 25% from baseline, an increased percentage of subjects with on-treatment PR greater than 200 msec, or an increased risk of adverse reactions 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.

4.5 Interaction with other medicinal products and other forms of interaction

Since pregabalin are predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (less than 2% of a doss recovered in urine as matabolites), and does not bind to plasma proteins, Its pharmacokinetics are unlikely to be affected by other agent through metabolic interactions or protein binding displacement. *In vitro* and *in vivo* studies showed that pregabalin are 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 (see section 5.1).

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 capsules was co-administered with these drugs.

No clinically important effects on respiration were seen.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data for the use of pregabalin in pregnant women.

Study in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Pregabalin should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the foetus).

Breastfeeding

Pregabalin is execrated into human milk. The effect of pregabalin on infants is unknown.

Fertility

There are no clinical data on the effect 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.

A fertility study in female rats has shown adverse reproductive effects. Fertility studies in male rats have shown adverse reproductive and developmental effects. The clinical relevance of these findings is unknown.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Clinical Study

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.

The most commonly reported adverse reactions in all controlled clinical studies presented in Table 4.

Table 4. Pregabalin adverse drug reactions

System organ class	Adverse drug reactions (controlled clinical studies)				
	Neuropathic pain associated with diabetic peripheral neuropathy	**Postherpetic neuralgia**	**Partial-onset seizures (adult)**	**Fibromyalgia**	**Neuropathic pain associated with spinal cord injury**
Body as a whole	Asthenia	Infection	Accidental injury	-	-
	Accidental injury	Headache	Pain	-	-
	Back pain	Pain	-	-	-
	Chest pain	Accidental injury	-	-	-
	Face edema	Flu syndrome	-	-	-
	-	Face edema	-	-	-
Infections and infestations	-	-	-	Sinusitis	-
Metabolic and nutritional disorders	Peripheral edema	Peripheral edema	Peripheral edema	increased appetite	-
	Weight gain	Weight gain	Weight gain	Fluid retention	-
	Edema	Edema	-	-	-
	Hypoglycemia	-	-	-	-
Psychiatric disorders	-	-	-	Euphoric Mood	Insomnia
	-	-	-	Confusional state	Euphoric mood
	-	-	-	Anxiety	-
	-	-	-	Disorientation	-
	-	-	-	Depression	-
Nervous system	Dizziness	Dizziness	Dizziness	Dizziness	Dizziness
	Somnolence	Somnolence	Somnolence	Somnolence	Somnolence
	Neuropathy	Ataxia	Ataxia	Headache	Disturbance in attention
	Ataxia	Abnormal gait	Tremor	Disturbance in attention	Memory impairment
	Vertigo	Confusion	Incoordination	Balance disorder	Paresthesia
	Confusion	Incoordination	Amnesia	Memory impairment	-
	Euphoria	Amnesia	Speech disorder	Coordination abnormal	-
	Incoordination	Speech disorder	Incoordination	Hypoesthesia	-
	Tremor	-	Abnormal gait	Lethargy	-
	Abnormal gait	-	Twitching	Tremor	-
	Amnesia	-	Confusion	-	-

	Nervousness	-	Myoclonus	-	-
	Dry mouth	Dry mouth	Increased Appetite	Dry mouth	Dry mouth
Eye disorders	-	-	-	Vision blurred	Vision blurred
Ear and labyrinth disorders	-	-	-	Vertigo	Vertigo
Vascular disorders	-	-	-	-	Hypertension
	-	-	-	-	Hypotension
Respiratory, thoracic and mediastinal disorders	Dyspnea	Bronchitis	-	Pharyngolaryngeal pain	-
Gastrointestinal system	Constipation	Constipation	Dry mouth	Constipation	Constipation
	Flatulence	Flatulence	Constipation	Flatulence	Nausea
	-	Vomiting	-	Vomiting	Vomiting
Skin and subcutaneous tissue disorders	-	-	-	-	Decubitus ulcer
Musculoskeletal and connective tissue disorders	-	Myasthenia	-	Arthralgia	Muscular weakness
	-	-	-	Muscle spasms	Pain in extremity
	-	-	-	Back pain	Neck pain
	-	-	-	-	Back pain
	-	-	-	-	Joint swelling
Renal and urinary disorders	-	-	-	-	Urinary incontinence
	-	Urinary Incontinence	-	-	-
General disorders and administrative site conditions	-	-	-	Fatigue	Fatigue
	-	-	-	Edema peripheral	Edema peripheral
	-	-	-	Chest pain	Edema
	-	-	-	Feeling abnormal	Pain
	-	-	-	Edema	-
	-	-	-	Feeling drunk	-
Investigations	-	-	-	Weight increased	Weight increased
	-	-	-	-	Blood creatine phosphokinase increased
Special senses	Blurry vision	Blurry vision	Blurry vision	-	-
	Abnormal vision	Abnormal vision	Abnormal vision	-	-
	-	Diplopia	Diplopia	-	-
	-	Eye Disorder	-	-	-

Other adverse reactions observed during the clinical studies of pregabalin

In table 5 below adverse reactions 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).

Table 5. Pregabalin adverse drug reactions

System Organ Class	**Adverse drug reactions**
Body as a whole	
Common	Abdominal pain, Allergic reaction, Fever
Uncommon	Abscess, Cellulitis, Chills, Malaise, Neck rigidity, Overdose, Pelvic pain, Photosensitivity reaction
Rare	Anaphylactoid reaction, Ascites, Granuloma, Hangover effect, Intentional Injury, Retroperitoneal Fibrosis, Shock
Blood and lymphatic system disorders	
Common	Ecchymosis
Uncommon	Anemia, Eosinophilia, Hypochromic anemia, Leukocytosis, Leukopenia, Lymphadenopathy, Thrombocytopenia
Rare	Myelofibrosis, Polycythemia, Prothrombin decreased, Purpura, Thrombocythemia, Alanine aminotransferase increased, Aspartate aminotransferase increased
Metabolic and nutritional disorders	
Rare	Glucose Tolerance Decreased, Urate Crystalluria
Nervous system disorders	
Common	Anxiety, Depersonalization, Hypertonia, Hypoesthesia, Libido decreased, Nystagmus, Paresthesia, Sedation, Stupor, Twitching
Uncommon	Abnormal dreams, Agitation, Apathy, Aphasia, Circumoral paresthesia, Dysarthria, Hallucinations, Hostility, Hyperalgesia, Hyperesthesia, Hyperkinesia, Hypokinesia, Hypotonia, Libido increased, Myoclonus, Neuralgia
Rare	Addiction, Cerebellar syndrome, Cogwheel rigidity, Coma, Delirium, Delusions, Dysautonomia, Dyskinesia, Dystonia, Encephalopathy, Extrapyramidal syndrome, Guillain-Barré syndrome, Hypalgesia, Intracranial hypertension, Manic reaction, Paranoid reaction, Peripheral neuritis, Personality disorder, Psychotic depression, Schizophrenic reaction, Sleep disorder, Torticollis, Trismus
Not known	Headache
Cardiac disorders	
Uncommon	Deep thrombophlebitis, Heart failure, Hypotension, Postural hypotension, Retinal vascular disorder, Syncope
Rare	ST Depressed, Ventricular Fibrillation
Respiratory, thoracic and mediastinal disorders	
Rare	Apnea, Atelectasis, Bronchiolitis, Hiccup, Laryngismus, Lung edema, Lung fibrosis, Yawn
Gastrointestinal disorders	
Common	Gastroenteritis, Increased appetite
Uncommon	Cholecystitis, Cholelithiasis, Colitis, Dysphagia, Esophagitis, Gastritis, Gastrointestinal hemorrhage, Melena, Mouth ulceration, Pancreatitis, Rectal hemorrhage, Tongue edema.
Rare	Aphthous stomatitis, Esophageal Ulcer, Periodontal abscess
Not known	Nausea, Diarrhea
Skin and subcutaneous tissue disorders	

Common	Pruritus, Alopecia, Dry skin, Eczema, Hirsutism, Skin ulcer, Urticaria, Vesiculobullous rash
Rare	Angioedema, Exfoliative dermatitis, Lichenoid dermatitis, Melanosis, Nail Disorder, Petechial rash, Purpuric rash, Pustular rash, Skin atrophy, Skin necrosis, Skin nodule, Stevens-Johnson syndrome, Subcutaneous nodule
Not known	Bullous pemphigoid
Musculoskeletal and connective tissue disorders	
Common	Arthralgia, Leg cramps, Myalgia, Myasthenia
Uncommon	Arthrosis
Rare	Chondrodystrophy, Generalized Spasm
Renal and urinary disorders	
Common	Anorgasmia, Impotence, Urinary frequency, Urinary incontinence
Uncommon	Abnormal ejaculation, Albuminuria, Amenorrhea, Dysmenorrhea, Dysuria, Hematuria, Kidney calculus, Leukorrhea, Menorrhagia, Metrorrhagia, Nephritis, Oliguria, Urinary retention, Urine abnormality
Rare	Acute kidney failure, Balanitis, Bladder Neoplasm, Cervicitis, Dyspareunia, Epididymitis, Female lactation, Glomerulitis, Ovarian disorder, Pyelonephritis
Reproductive system and breast disorders	
Not known	Gynecomastia, Breast Enlargement
Special senses	
Common	Conjunctivitis, Diplopia, Otitis media, Tinnitus
Uncommon	Abnormality of accommodation, Blepharitis, Dry eyes, Eye hemorrhage, Hyperacusis, Photophobia, Retinal edema, Taste loss, Taste perversion
Rare	Anisocoria, Blindness, Corneal ulcer, Exophthalmos, Extraocular palsy, Iritis, Keratitis, Keratoconjunctivitis, Miosis, Mydriasis, Night blindness, Ophthalmoplegia, Optic atrophy, Papilledema, Parosmia, Ptosis, Uveitis

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the local reporting system.

4.9 Overdose

Signs, symptoms and laboratory findings of acute overdosage in humans

In the postmarketing experience, the most commonly reported adverse events observed with pregabalin when taken in overdose include reduced consciousness, depression/anxiety, confusional state, agitation, and restlessness. Seizures and heart block have also been reported. Deaths have been reported in the setting of lone pregabalin overdose and in combination with other CNS depressants.

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.

Pregabalin can be removed by hemodialysis. Standard hemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Gabapentinoids

ATC code: N02BF01

The active substance, pregabalin, is a gamma-aminobutyric acid analogue [(S)-3-(aminomethyl)-5-methylhexanoic acid].

Mechanism of action and pharmacodynamics effects

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

While pregabalin is a structural derivative of the inhibitory neurotransmitter gamma-aminobutyric 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.

Clinical efficacy and safety

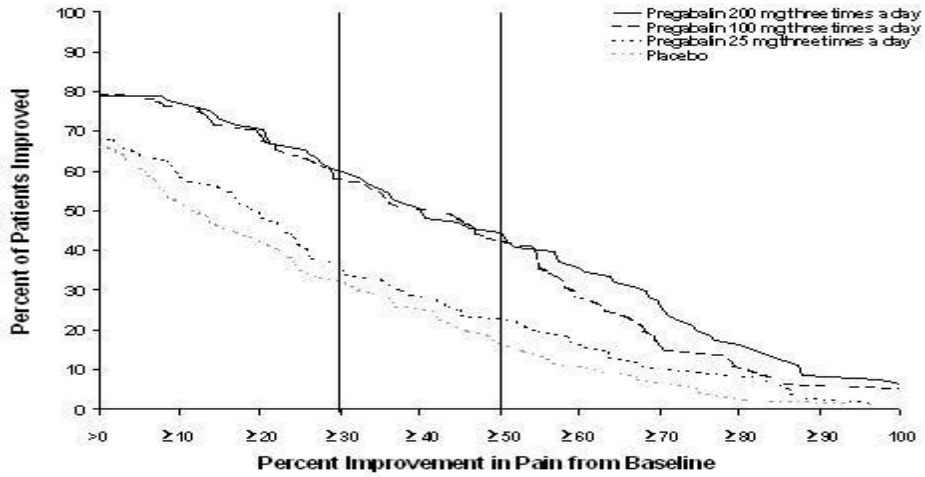
Neuropathic pain associated with diabetic peripheral neuropathy

The efficacy of the maximum recommended dose of pregabalin for the management of neuropathic pain associated with diabetic peripheral neuropathy was established in three double-blind, placebo-controlled, multicenter studies with three times a day dosing, two of which studied the maximum recommended dose. Patients were enrolled with either Type 1 or Type 2 diabetes mellitus and a diagnosis of painful distal symmetrical sensorimotor polyneuropathy for 1 to 5 years. A total of 89% of patients completed Studies DPN 1 and DPN 2. The patients had a minimum mean baseline pain score of greater than or equal to 4 on an 11-point numerical pain rating scale ranging from 0 (no pain) to 10 (worst possible pain). The baseline mean pain scores across the two studies ranged from 6.1 to 6.7. Patients were permitted up to 4 grams of acetaminophen per day as needed for pain, in addition to pregabalin. Patients recorded their pain daily in a diary.

Study DPN 1: This 5-week study compared pregabalin 25, 100, or 200 mg three times a day with placebo. Treatment with pregabalin 100 and 200 mg three times a day statistically significantly improved the endpoint mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline. There was no evidence of a greater effect on pain scores of the 200 mg three times a day dose than the 100 mg three times a day dose, but there was evidence of dose dependent adverse reactions (see section 4.8). For a range of levels of improvement in pain intensity from baseline to study endpoint, figure 1 shows the fraction of patients achieving that level of improvement. The figure is cumulative, so that patients whose change from baseline is, for example,

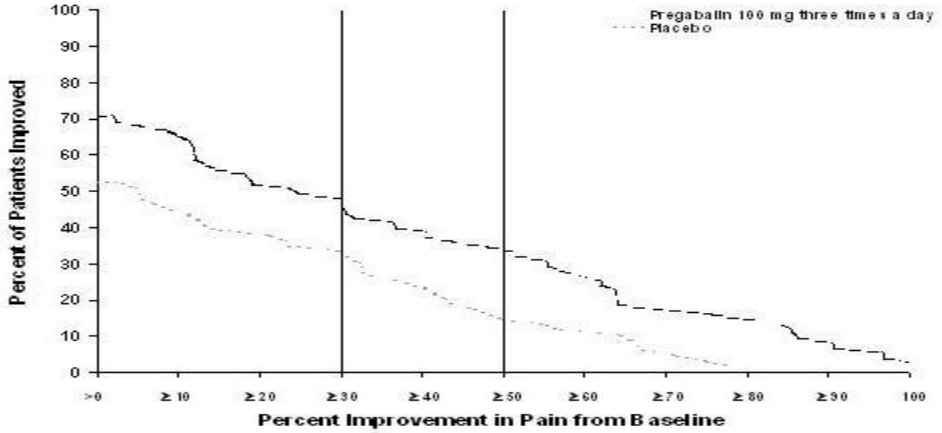
50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

Figure 1: Patients achieving various levels of improvement in pain intensity – study DPN 1



Treatment with pregabalin 100 mg three times a day statistically significantly improved the endpoint mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline. For various levels of improvement in pain intensity from baseline to study endpoint, Figure 2 shows the fraction of patients achieving that level of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

Figure 2: Patients achieving various levels of improvement in pain intensity– study DPN 2

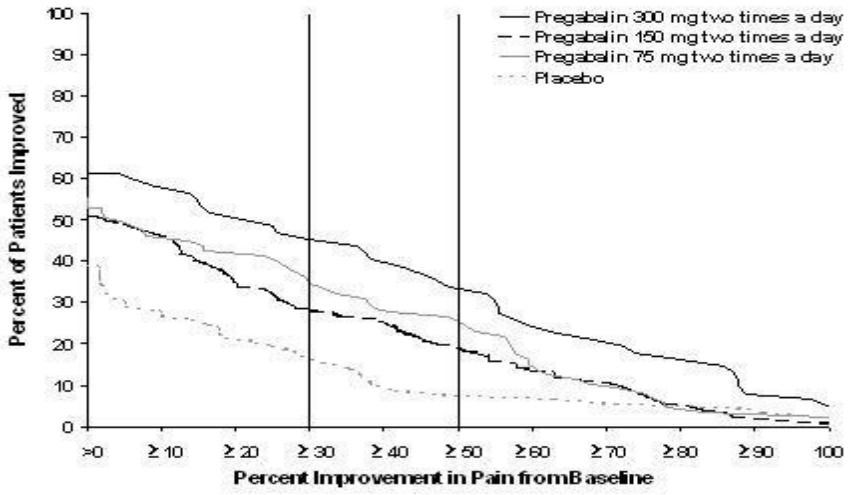


Postherpetic neuralgia

The efficacy of pregabalin for the management of postherpetic neuralgia was established in three double-blind, placebo-controlled, multicenter studies. These studies enrolled patients with neuralgia persisting for at least 3 months following healing of herpes zoster rash and a minimum baseline score of greater than or equal to 4 on an 11-point numerical pain rating scale ranging from 0 (no pain) to 10 (worst possible pain). Seventy-three percent of patients completed the studies. The baseline mean pain scores across the 3 studies ranged from 6 to 7. Patients were permitted up to 4 grams of acetaminophen per day as needed for pain, in addition to pregabalin. Patients recorded their pain daily in a diary.

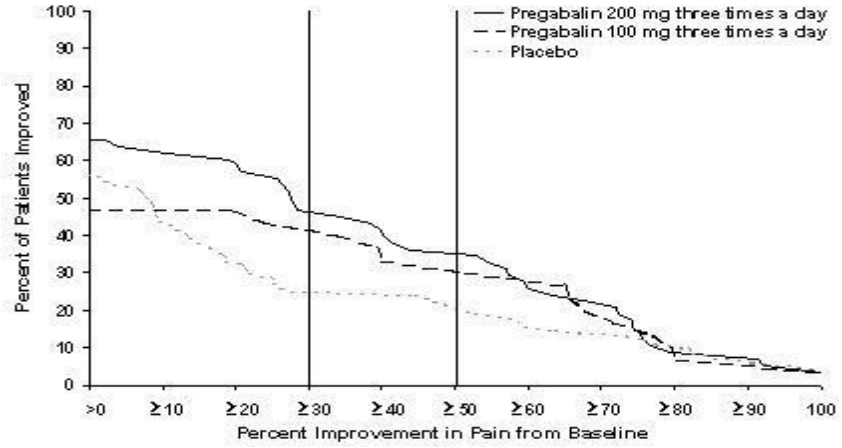
Study PHN 1: This 13-week study compared pregabalin 75, 150, and 300 mg twice daily with placebo. Patients with creatinine clearance (CLcr) between 30 to 60 mL/min were randomized to 75 mg, 150 mg, or placebo twice daily. Patients with creatinine clearance greater than 60 mL/min were randomized to 75 mg, 150 mg, 300 mg or placebo twice daily. In patients with creatinine clearance greater than 60 mL/min treatment with all doses of pregabalin statistically significantly improved the endpoint mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline. Despite differences in dosing based on renal function, patients with creatinine clearance between 30 to 60 mL/min tolerated pregabalin less well than patients with creatinine clearance greater than 60 mL/min as evidenced by higher rates of discontinuation due to adverse reactions. For various levels of improvement in pain intensity from baseline to study endpoint, Figure 3 shows the fraction of patients achieving that level of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

Figure 3: Patients achieving various levels of improvement in pain intensity– study PHN 1



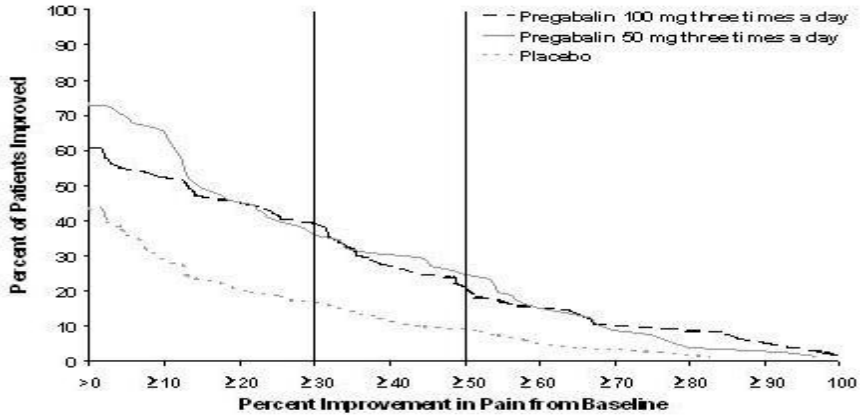
Study PHN 2: This 8-week study compared pregabalin 100 or 200 mg three times a day with placebo, with doses assigned based on creatinine clearance. Patients with creatinine clearance between 30 to 60 mL/min were treated with 100 mg three times a day, and patients with creatinine clearance greater than 60 mL/min were treated with 200 mg three times daily. Treatment with pregabalin statistically significantly improved the endpoint mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline. For various levels of improvement in pain intensity from baseline to study endpoint, Figure 4 shows the fraction of patients achieving those levels of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

Figure 4: Patients achieving various levels of improvement in pain intensity – study PHN 2



Study PHN 3: This 8-week study compared pregabalin 50 or 100 mg three times a day with placebo with doses assigned regardless of creatinine clearance. Treatment with pregabalin 50 and 100 mg three times a day statistically significantly improved the endpoint mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline. Patients with creatinine clearance between 30 to 60 mL/min tolerated pregabalin less well than patients with creatinine clearance greater than 60 mL/min as evidenced by markedly higher rates of discontinuation due to adverse reactions. For various levels of improvement in pain intensity from baseline to study endpoint, Figure 5 shows the fraction of patients achieving that level of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

Figure 5: Patients achieving various levels of improvement in pain intensity– study PHN 3



Adjunctive therapy for partial-onset seizures in adult patients

The efficacy of pregabalin as adjunctive therapy for partial-onset seizures in adult patients was established in three 12-week, randomized, double-blind, placebo-controlled, multicenter studies. Patients were enrolled who had partial-onset seizures with or without secondary generalization and were not adequately controlled with 1 to 3 concomitant antiepileptic drugs (AEDs). Patients taking gabapentin were required to discontinue gabapentin treatment 1 week prior to entering baseline. During an 8-week baseline period, patients had to experience at least 6 partial-onset seizures with no seizure-free period exceeding 4 weeks. The mean duration of epilepsy was 25 years in these 3 studies and the mean and median baseline seizure frequencies were 22.5 and 10 seizures per month, respectively. Approximately half of the patients were taking 2 concurrent AEDs at baseline. Among the pregabalin-treated patients, 80% completed the double-blind phase of the studies.

Table 6 shows median baseline seizure rates and median percent reduction in seizure frequency by dose.

Table 6. Seizure response in controlled, adjunctive epilepsy studies in adults

Daily dose of pregabalin	Dosing regimen	N	Baseline seizure frequency/mo	Median % change from baseline	p-value, vs. placebo
Study E1					
Placebo	BID	100	9.5	0	
50 mg/day	BID	88	10.3	-9	0.4230
150 mg/day	BID	86	8.8	-35	0.0001
300 mg/day	BID	90	9.8	-37	0.0001
600 mg/day	BID	89	9.0	-51	0.0001
Study E2					
Placebo	TID	96	9.3	1	
150 mg/day	TID	99	11.5	-17	0.0007
600 mg/day	TID	92	12.5	-43	0.0001
Study E3					
Placebo	BID/TID	98	11	-1	
600 mg/day	BID	103	9.5	-36	0.0001
600 mg/day	TID	111	10	-48	0.0001

In the first study (E1), there was evidence of a dose-response relationship for total daily doses of pregabalin between 150 and 600 mg/day; a dose of 50 mg/day was not effective. In the first study (E1), each daily dose was divided into two equal doses (twice a day dosing). In the second study (E2), each daily dose was divided into three equal doses (three times a day dosing). In the third study (E3), the same total daily dose was divided into two equal doses for one group (twice a day dosing) and three equal doses for another group (three times a day dosing). While the three times a day dosing group in Study E3 performed numerically better than the twice a day dosing group, this difference was small and not statistically significant.

A secondary outcome measure included the responder rate (proportion of patients with greater than or equal to 50% reduction from baseline in partial seizure frequency). The following figure displays responder rate by dose for two of the studies.

Figure 6: Responder rate by adjunctive epilepsy study

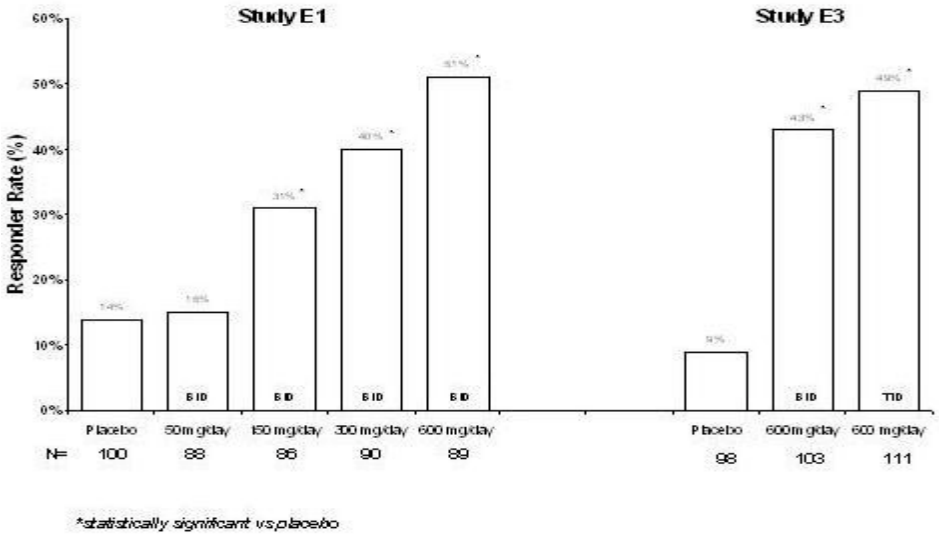
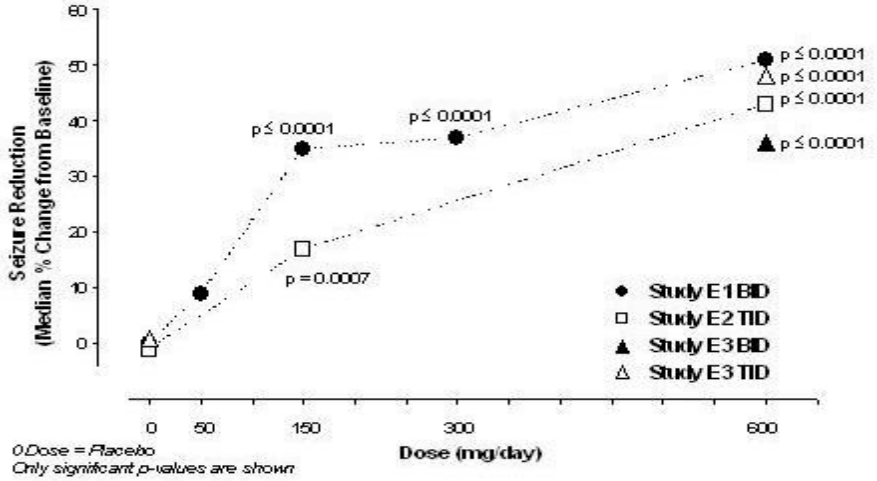


Figure 7: Seizure reduction by dose (all partial-onset seizures) for studies e1, e2, and e3



Subset evaluations of the antiseizure efficacy of pregabalin showed no clinically important differences as a function of age, gender, or race.

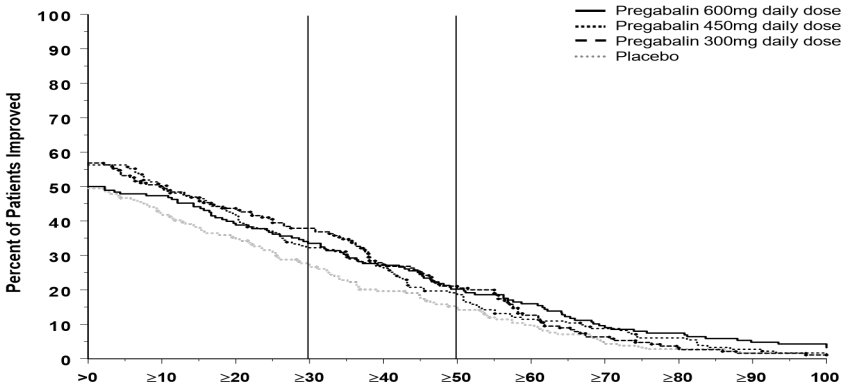
Management of fibromyalgia

The efficacy of pregabalin for management of fibromyalgia was established in one 14-week, double-blind, placebo-controlled, multicenter study (F1) and one six-month, randomized withdrawal study (F2). Studies F1 and F2 enrolled patients with a diagnosis of fibromyalgia using the American College of Rheumatology (ACR) criteria (history of widespread pain for 3 months, and pain present at 11 or more of the 18 specific tender point sites). The studies showed a reduction in pain by visual analog scale. In addition, improvement was demonstrated based on a patient global assessment (PGIC), and on the fibromyalgia impact questionnaire (FIQ).

Study F1: This 14-week study compared pregabalin total daily doses of 300 mg, 450 mg and 600 mg with placebo. Patients were enrolled with a minimum mean baseline pain score of greater than or equal to 4 on an 11-point numeric pain rating scale and a score of greater than or equal to 40 mm on the 100 mm pain visual analog scale (VAS). The baseline mean pain score in this trial was 6.7. Responders to placebo in an initial one-week run-in phase were not randomized into subsequent phases of the study. A total of 64% of patients randomized to pregabalin completed the study. There was no evidence of a greater effect on pain scores of the 600 mg daily dose than the 450 mg daily dose, but there was evidence of dose-dependent adverse reactions (see section 4.8). Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study. The results are summarized in figure 8 and Table 7.

For various levels of improvement in pain intensity from baseline to study endpoint, figure 8 shows the fraction of patients achieving that level of improvement. The figure is cumulative. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

Figure 8: Patients achieving various levels of improvement in pain intensity-fibromyalgia study F1



Percent improvement in pain from baseline

Table 7. Patient global response in fibromyalgia study F1

Patient Global Impression of Change		
Treatment group (mg/day)	**% Any improvement**	**95% CI**
Placebo	47.6	(40.0,55.2)
PGB 300	68.1	(60.9, 75.3)
PGB 450	77.8	(71.5, 84.0)
PGB 600	66.1	(59.1, 73.1)

PGB = Pregabalin

Study F2: This randomized withdrawal study compared pregabalin with placebo. Patients were titrated during a 6-week open-label dose optimization phase to a total daily dose of 300 mg, 450 mg, or 600 mg. Patients were considered to be responders if they had both: 1) at least a 50% reduction in pain (VAS) and, 2) rated their overall improvement on the PGIC as "much improved" or "very much improved." Those who responded to treatment were then randomized in the double-blind treatment phase to either the dose achieved in the open-label phase or to placebo. Patients were treated for up to 6 months following randomization. Efficacy was assessed by time to loss of therapeutic response, defined as 1) less than 30% reduction in pain (VAS) from open-label baseline during two consecutive visits of the double-blind phase, or 2) worsening of FM symptoms necessitating an alternative treatment. Fifty-four percent of patients were able to titrate to an effective and tolerable dose of pregabalin during the 6-week open-label phase. Of the patients entering the randomized treatment phase assigned to remain on pregabalin, 38% of patients completed 26 weeks of treatment versus 19% of placebo-treated patients.

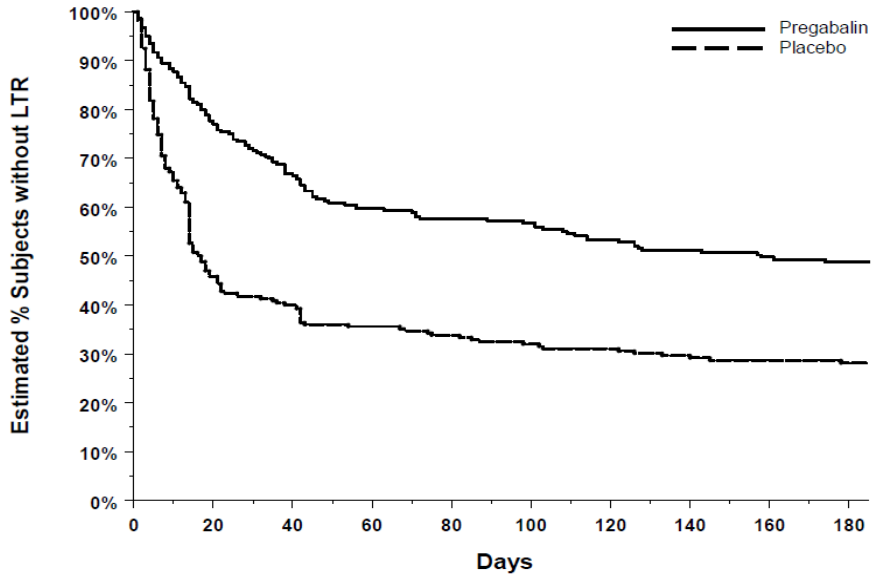
When considering return of pain or withdrawal due to adverse events as loss of response (LTR), treatment with pregabalin resulted in a longer time to loss of therapeutic response than treatment with placebo. Fifty-three percent of the pregabalin-treated subjects compared to 33% of placebo.

patients remained on study drug and maintained a therapeutic response to week 26 of the study. Treatment with pregabalin also resulted in a longer time to loss of response based on the FIQ[1], and longer time to loss of overall assessment of patient status, as measured by the PGIC[2].

[1] Time to worsening of the FIQ was defined as the time to a 1-point increase from double-blind baseline in each of the subscales, and a 5-point increase from double-blind baseline evaluation for the FIQ total score.

[2] Time to PGIC lack of improvement was defined as time to PGIC assessments indicating less improvement than “much improvement.”

Figure 9: Time to loss of therapeutic response, fibromyalgia study F2 (kaplan-meier analysis)



Management of neuropathic pain associated with spinal cord injury

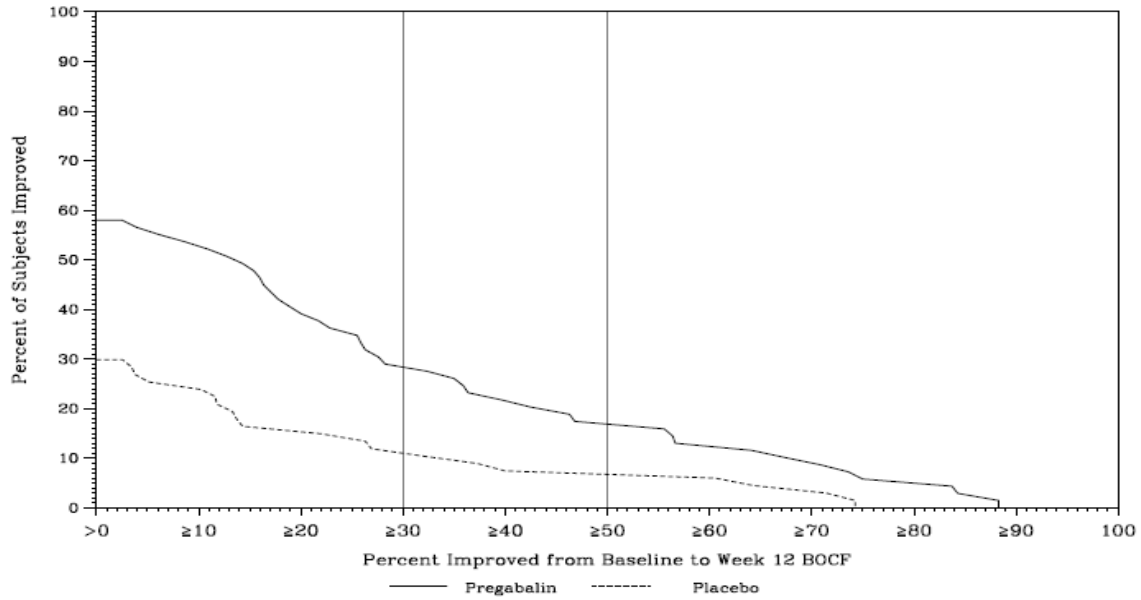
The efficacy of pregabalin for the management of neuropathic pain associated with spinal cord injury was established in two double-blind, placebo-controlled, multicenter studies. Patients were enrolled with neuropathic pain associated with spinal cord injury that persisted continuously for at least three months or with relapses and remissions for at least six months. A total of 63% of patients completed study 1 and 84% completed study 2. The patients had a minimum mean baseline pain score of greater than or equal to 4 on an 11-point numerical pain rating scale.

ranging from 0 (no pain) to 10 (worst possible pain). The baseline mean pain scores across the two studies ranged from 6.5 to 6.7.

Patients were allowed to take opioids, non-opioid analgesics, antiepileptic drugs, muscle relaxants, and antidepressant drugs if the dose was stable for 30 days prior to screening. Patients were allowed to take acetaminophen and nonsteroidal anti-inflammatory drugs during the studies.

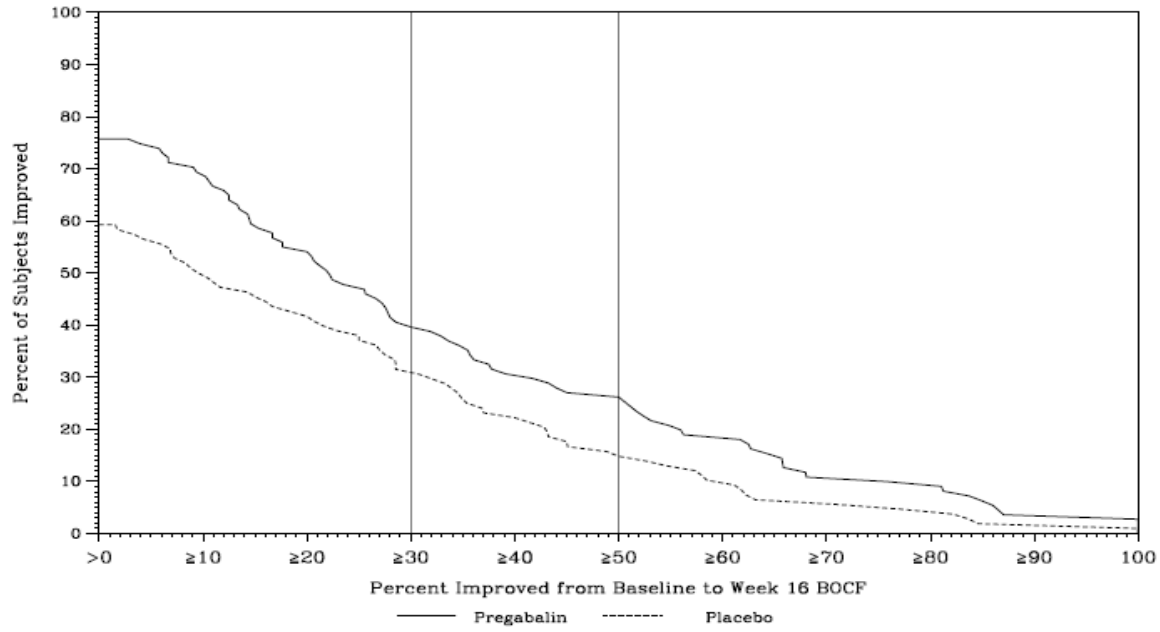
Study SCI 1: This 12-week, randomized, double-blind, parallel-group, multicenter, flexible dose (150-600 mg/day) study compared pregabalin with placebo. The 12-week study consisted of a 3-week dose adjustment phase and a 9-week dose maintenance phase. Treatment with pregabalin 150-600 mg/day statistically significantly improved the endpoint weekly mean pain score, and increased the proportion of patients with at least a 30% and 50% reduction in pain score from baseline. The fraction of patients achieving various levels of improvement in pain intensity from baseline to week 12 is presented in figure 10. Some patients experienced a decrease in pain as early as week 1, which persisted throughout the study.

Figure 10: Patients achieving various levels of improvement in pain intensity – study SCI 1



Study SCI 2: This 16-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter, flexible dose (150-600 mg/day, in increments of 150 mg) study compared the efficacy, safety and tolerability of pregabalin with placebo. The 16-week study consisted of a 4-week dose adjustment phase and a 12-week dose maintenance phase. Treatment with pregabalin statistically significantly improved the endpoint weekly mean pain score, and increased the proportion of patients with at least a 30% and 50% reduction in pain score from baseline. The fraction of patients achieving various levels of improvement in pain intensity from baseline to week 16 is presented in figure 11. Some patients experienced a decrease in pain as early as week 1, which persisted throughout the study.

Figure 11: Patients achieving various levels of improvement in pain intensity – Study SCI 2



5.2 Pharmacokinetic properties

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 greater than or equal to 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. Multiple-dose pharmacokinetics can be predicted from single-dose data.

The rate of pregabalin absorption is decreased when given with food, resulting in a decrease in C_{max} of approximately 25% 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. 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.

Biotransformation 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 (S-enantiomer) did not undergo racemization to the R-enantiomer in mice, rats, rabbits, or monkeys.

Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug with a mean elimination half-life of 6.3 hours in subjects with normal renal function. Mean renal clearance was estimated to be 67.0 to 80.9 mL/min in young healthy subjects. Because pregabalin is not bound to plasma proteins this clearance rate indicates that renal tubular reabsorption is involved. Pregabalin elimination is nearly proportional to creatinine clearance (CLcr) (see section 4.2)

5.3 Preclinical safety data

Carcinogenesis

A dose-dependent increase in the incidence of malignant vascular tumors (hemangiosarcomas) was observed in two strains of mice (B6C3F1 and CD-1) given pregabalin (200, 1000, or 5000 mg/kg) in the diet for two years. Plasma pregabalin exposure (AUC) in mice receiving the lowest dose that increased hemangiosarcomas was approximately equal to the human exposure at the maximum recommended dose (MRD) of 600 mg/day. A no-effect dose for induction of hemangiosarcomas in mice was not established. No evidence of carcinogenicity was seen in two studies in wistar rats following dietary administration of pregabalin for two years at doses (50, 150, or 450 mg/kg in males and 100, 300, or 900 mg/kg in females) that were associated with plasma exposures in males and females up to approximately 14 and 24 times, respectively, human exposure at the MRD.

Mutagenesis

Pregabalin was not mutagenic in bacteria or in mammalian cells *in vitro*, was not clastogenic in mammalian systems *in vitro* and *in vivo*, and did not induce unscheduled DNA synthesis in mouse or rat hepatocytes.

Impairment of fertility

In fertility studies in which male rats were orally administered pregabalin (50 to 2500 mg/kg) prior to and during mating with untreated females, a number of adverse reproductive and developmental effects were observed. These included decreased sperm counts and sperm motility, increased sperm abnormalities, reduced fertility, increased preimplantation embryo loss, decreased litter size, decreased fetal body weights, and an increased incidence of fetal abnormalities. Effects on sperm and fertility parameters were reversible in studies of this duration (3–4 months). The no-effect dose for male reproductive toxicity in these studies (100 mg/kg) was associated with a plasma pregabalin exposure (AUC) approximately 3 times human exposure at the maximum recommended dose (MRD) of 600 mg/day.

In addition, adverse reactions on reproductive organ (testes, epididymides) histopathology were observed in male rats exposed to pregabalin (500 to 1250 mg/kg) in general toxicology studies of four weeks or greater duration. The no-effect dose for male reproductive organ histopathology in rats (250 mg/kg) was associated with a plasma exposure approximately 8 times human exposure at the MRD.

In a fertility study in which female rats were given pregabalin (500, 1250, or 2500 mg/kg) orally prior to and during mating and early gestation, disrupted estrous cyclicity and an increased number of days to mating were seen at all doses, and embryolethality occurred at the highest dose. The low dose in this study produced a plasma exposure approximately 9 times that in humans receiving the MRD. A no-effect dose for female reproductive toxicity in rats was not established.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Starch,

Talc

Capsule shell

For 50 mg and 150 mg strengths

Gelatin, purified water, sodium lauryl sulfate and titanium dioxide.

For 75 mg strength

FD &C Blue 1, FD&C: Red 40, FD& C Yellow 6, gelatin, purified water, sodium lauryl sulfate and titanium dioxide.

Imprinting ink

For 50 mg, 75 mg and 150 mg strengths

Black iron oxide, potassium hydroxide, propylene glycol, purified water and shellac.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30° C

6.5 Nature and contents of container

Aluminium blister with PVC/PE/PVDC film (clear PVC film with PE, PVDC film)

Carton containing 3 blisters of 10 tablets.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Cipla Ltd India]

8. MARKETING AUTHORISATION NUMBER(S)

NA

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

NA

10. DATE OF REVISION OF THE TEXT

Sept 2023