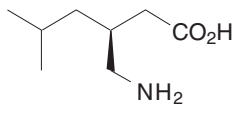
DESCRIPTION

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



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

LYRICA (pregabalin) Capsules are supplied as imprinted hard-shell capsules containing 25, 50, 75, 100, 150, 200, 225, and 300 mg of pregabalin, along with lactose monohydrate, cornstarch, and talc as inactive ingredients. The capsule shells contain gelatin and titanium dioxide. In addition, the orange capsule shells contain red iron oxide and the white capsule shells contain sodium lauryl sulfate and colloidal silicon dioxide. Colloidal silicon dioxide is a manufacturing aid that may or may not be present in the capsule shells. The imprinting ink contains shellac, black iron oxide, propylene glycol, and potassium hydroxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

LYRICA (pregabalin) binds with high affinity to the alpha$_2$-delta site (an auxiliary subunit of voltage-gated calcium channels) in central nervous system tissues. Although the mechanism of action of pregabalin is unknown, results with genetically modified mice and with compounds structurally related to pregabalin (such as gabapentin) suggest that binding to the alpha$_2$-delta subunit may be involved in pregabalin's antinociceptive and antiseizure effects in animal models. *In vitro*, pregabalin reduces the calcium-dependent release of several neurotransmitters, possibly by modulation of calcium channel function.

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.

Pharmacokinetics

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

Absorption and Distribution

Following oral administration of pregabalin capsules under fasting conditions, peak plasma concentrations occur within 1.5 hours. Pregabalin oral bioavailability is ≥90% and is independent of dose. Following single- (25 to 300 mg) and multiple-dose (75 to 900 mg/day) administration, maximum plasma concentrations (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.

Metabolism and Elimination

Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabeled pregabalin, approximately 90% of the administered dose was recovered in the urine as unchanged pregabalin. The N-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0.9% of the dose. In preclinical studies, pregabalin (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 **Special Populations, Renal Impairment and DOSAGE AND ADMINISTRATION, Patients with Impaired Renal Function).**

Special Populations

Race: In population pharmacokinetic analyses of the clinical studies in various populations, the pharmacokinetics of pregabalin were not significantly affected by race (Caucasians, Blacks, and Hispanics).

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

Renal Impairment and Hemodialysis: Pregabalin clearance is nearly proportional to creatinine clearance (CLcr). Dosage reduction in patients with renal dysfunction is necessary. Pregabalin is effectively removed from plasma by hemodialysis. Following a 4-hour hemodialysis treatment, plasma pregabalin concentrations are reduced by approximately 50%. For patients on hemodialysis, dosing must be modified (see **DOSAGE AND ADMINISTRATION, Patients with Renal Impairment).**

Elderly: Pregabalin oral clearance tended to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with age-related decreases in CLcr. Reduction of pregabalin dose may be required in patients who have age-related compromised renal function (see **DOSAGE AND ADMINISTRATION, Patients with Renal Impairment).**

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

Drug Interactions:

***In Vitro* Studies:** Pregabalin, at concentrations that were, in general, 10-times those attained in clinical trials, does not inhibit human CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 enzyme systems. The potential of pregabalin to induce these enzymes has not been studied *in vitro.*

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

Gabapentin: The pharmacokinetic interactions of pregabalin and gabapentin were investigated in 12 healthy subjects following concomitant single-dose administration of 100-mg pregabalin and 300-mg gabapentin and in 18 healthy subjects following concomitant multiple-dose administration of 200-mg pregabalin every 8 hours and 400-mg gabapentin every 8 hours. Gabapentin pharmacokinetics following single- and multiple-dose administration were unaltered by pregabalin coadministration. The extent of pregabalin absorption was unaffected by gabapentin coadministration, although there was a small reduction in rate of absorption.

Oral Contraceptive: Pregabalin coadministration (200 mg three times a day) had no effect on the steady-state pharmacokinetics of norethindrone and ethinyl estradiol (1 mg/35 µg, respectively) in healthy subjects.

Lorazepam: Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects had no effect on the rate and extent of lorazepam single-dose pharmacokinetics and single-dose administration of lorazepam (1 mg) had no effect on the steady-state pharmacokinetics of pregabalin.

Oxycodone: Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects had no effect on the rate and extent of oxycodone single-dose pharmacokinetics. Single-dose administration of oxycodone (10 mg) had no effect on the steady-state pharmacokinetics of pregabalin.

Ethanol: Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects had no effect on the rate and extent of ethanol single-dose pharmacokinetics and single-dose administration of ethanol (0.7 g/kg) had no effect on the steady-state pharmacokinetics of pregabalin.

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

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

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

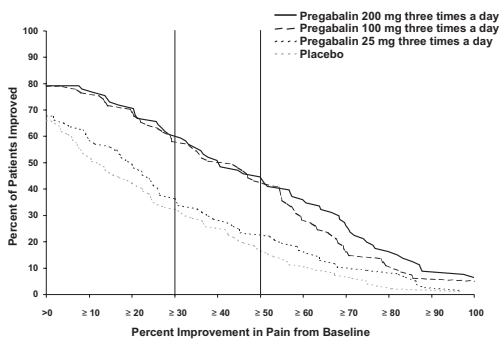
CLINICAL STUDIES

Neuropathic pain associated with diabetic peripheral neuropathy

The efficacy of the maximum recommended dose of LYRICA for the management of neuropathic pain associated with diabetic peripheral neuropathy was established in three double-blind, placebo-controlled, multicenter studies that enrolled 729 patients with three times a day dosing, two of which studied the maximum recommended dose. Studies DPN 1 and DPN 2 enrolled a total of 483 patients of which 89% completed the studies. Patients enrolled had Type 1 or 2 diabetes mellitus with a diagnosis of painful distal symmetrical sensorimotor polyneuropathy for 1 to 5 years. The patients had a minimum mean baseline pain score of ≥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.

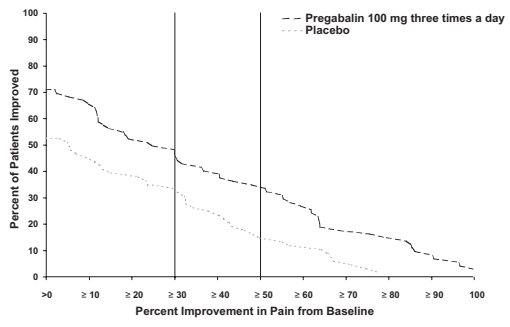
Study DPN 1: This 5-week study of 337 patients (240 pregabalin and 97 placebo) compared LYRICA 25, 100, or 200 mg three times a day with placebo. Treatment with LYRICA 100 and 200 mg three times a day statistically significantly improved the endpoint mean pain score and increased the proportion of patients 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 effects (see **ADVERSE REACTIONS).** For various degrees of improvement in pain from baseline to study endpoint, Figure 1 shows the fraction of patients achieving that degree 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 Pain Relief



Study DPN 2: This 8-week study of 146 patients (76 pregabalin and 70 placebo) compared LYRICA 100 mg three times a day with placebo. Treatment with LYRICA 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 degrees of improvement in pain from baseline to study endpoint, Figure 2 shows the fraction of patients achieving that degree 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 Pain Relief

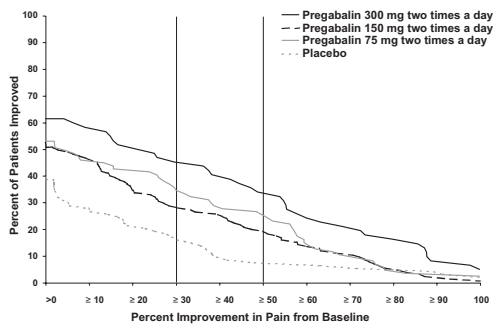


Postherpetic Neuralgia

The efficacy of LYRICA for the management of postherpetic neuralgia was established in three double-blind, placebo-controlled, multicenter studies. These studies enrolled 779 patients, of whom 566 completed the studies. These patients had neuralgia persisting for at least 3 months following healing of herpes zoster rash and a minimum baseline score of ≥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 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.

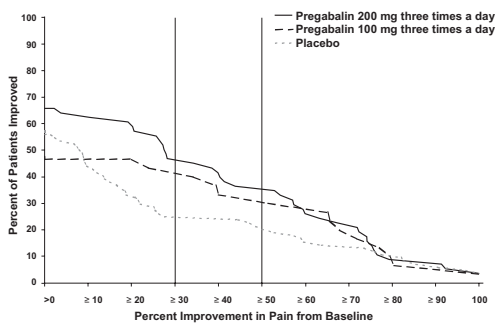
Study PHN 1: This 13-week study of 368 patients (275 pregabalin and 93 placebo) compared LYRICA 75, 150, and 300 mg twice daily with placebo. Patients with creatinine clearance (CLcr) between 30 to 60 mL/min were randomized to 75 mg, 150 mg, or placebo twice daily. Patients with creatinine clearance 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 LYRICA 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 LYRICA less well than patients with creatinine clearance greater than 60 mL/min as evidenced by higher rates of discontinuation due to adverse events. For various degrees of improvement in pain from baseline to study endpoint, Figure 3 shows the fraction of patients achieving that degree 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 Pain Relief



Study PHN 2: This 8-week study of 173 patients (89 pregabalin and 84 placebo) compared LYRICA 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 LYRICA 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 degrees of improvement in pain from baseline to study endpoint, Figure 4 shows the fraction of patients achieving that degree 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.

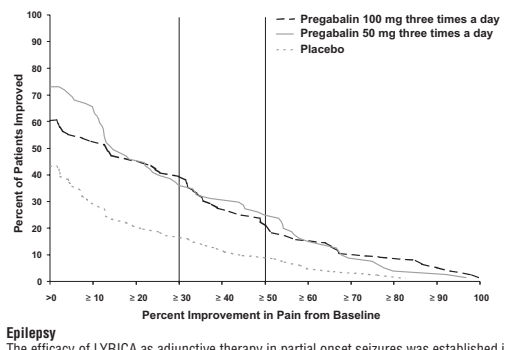
Figure 4: Patients Achieving Various Levels of Pain Relief



Study PHN 3: This 8-week study of 238 patients (157 pregabalin and 81 placebo) compared LYRICA 50 or 100 mg three times a day with placebo with doses assigned regardless of creatinine clearance. Treatment with LYRICA 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 LYRICA less well than patients with creatinine clearance greater than 60 mL/min as evidenced by markedly higher rates of discontinuation due to adverse events. For various degrees of improvement in pain from baseline to study endpoint, Figure 5 shows the fraction of patients achieving that degree 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.

CLINICAL STUDIES *(continued)*

Figure 5: Patients Achieving Various Levels of Pain Relief



Epilepsy

The efficacy of LYRICA as adjunctive therapy in partial onset seizures was established in three 12-week, randomized, double-blind, placebo-controlled, multicenter studies in 1052 adult patients. 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 LYRICA-treated patients, 80% completed the double-blind phase of the studies.

Table 1 shows median baseline seizure rates and median percent reduction in seizure frequency by dose.

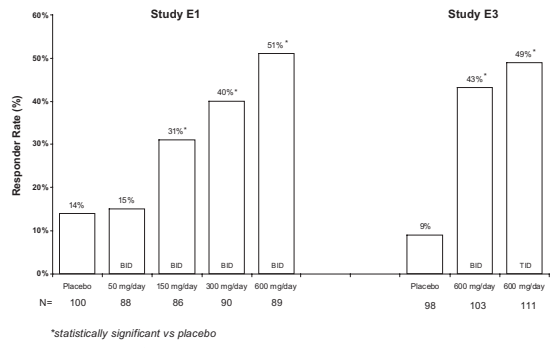
Table 1: Seizure Response in Controlled, Add-On Epilepsy Studies

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	12.3	-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 Lyrica 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.

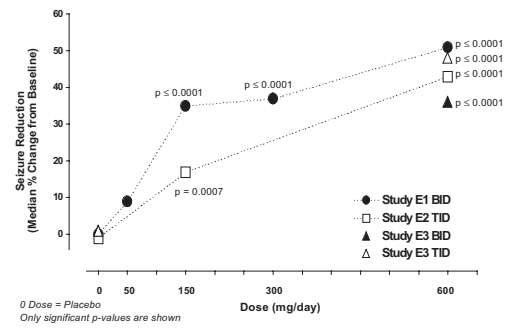
A secondary outcome measure included the responder rate (proportion of patients with ≥50% reduction from baseline in partial seizure frequency). The following figure displays responder rate by dose for two of the studies.

Figure 6: Responder rate by study



**statistically significant vs placebo*

Figure 7: Seizure Reduction by Dose (All Partial Onset Seizures) for Studies E1, E2, and E3



0 Dose = Placebo
Only significant p-values are shown

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

INDICATIONS AND USAGE

LYRICA is indicated for management of

- Neuropathic pain associated with diabetic peripheral neuropathy
- Postherpetic neuralgia

LYRICA is indicated as adjunctive therapy for adult patients with partial onset seizures.

CONTRAINDICATIONS

LYRICA is contraindicated in patients with known hypersensitivity to pregabalin or any of its components.

WARNINGS

Withdrawal of Antiepileptic Drugs (AEDs)

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

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 (see **PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility).** The clinical significance of this finding is unknown. Clinical experience during pregabalin's premarketing development provides no direct means to assess its potential for inducing tumors in humans.

In clinical studies across various patient populations, comprising 6396 patient-years of exposure in patients >12 years of age, new or worsening-preexisting tumors were reported in 57 patients. Without knowledge of the background incidence and recurrence in similar populations not treated with LYRICA, it is impossible to know whether the incidence seen in these cohorts is or is not affected by treatment.

PRECAUTIONS

Dizziness and Somnolence

Pregabalin causes dizziness and somnolence. Patients should be informed that pregabalin-related dizziness and somnolence may impair their ability to perform tasks such as driving or operating machinery (see **PRECAUTIONS-Information for Patients).**

In the pregabalin controlled trials, dizziness was experienced by 29% of pregabalin-treated patients compared to 9% of placebo-treated patients; somnolence was experienced by 22% of pregabalin-treated patients compared to 8% of placebo-treated patients. Dizziness and somnolence generally began shortly after the initiation of pregabalin therapy and occurred more frequently at higher doses. Dizziness and somnolence were the adverse events most frequently leading to withdrawal (4% each) from controlled studies. In pregabalin-treated patients reporting these adverse events in short-term, controlled studies, dizziness persisted until the last dose in 31% and somnolence persisted until the last dose in 46% of patients.

Ophthalmological Effects

In controlled studies, a higher proportion of patients treated with pregabalin reported blurred vision (6%) than did patients treated with placebo (2%), which resolved in a majority of cases with continued dosing. Less than 1% of patients discontinued pregabalin treatment due to vision-related events (primarily blurred vision).

Prospectively planned ophthalmologic testing, including visual acuity testing, formal visual field testing and dilated 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, patients should be informed that if changes in vision occur, they should notify their physician. If visual disturbance persists, further assessment should be considered. More frequent assessment should be considered for patients who are already routinely monitored for ocular conditions (See **PRECAUTIONS-Information for Patients).**

Abrupt or Rapid Discontinuation

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

Weight Gain

Pregabalin treatment caused weight gain. In pregabalin controlled clinical trials of up to 13 weeks, a gain of 7% or more over baseline weight was observed in 8% of pregabalin-treated patients and 2% of placebo-treated patients. Few patients treated with pregabalin (0.2%) withdrew from controlled trials due to weight gain. Pregabalin associated weight gain was related to dose and duration of exposure, but did not appear to be associated with baseline BMI, gender, or age. Weight gain was not limited to patients with edema (see **PRECAUTIONS-Peripheral 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 for at least 2 years, the average weight gain was 5.2 kg.

While the effects of pregabalin-associated weight gain on glycemic control have not been systematically assessed, in controlled and longer-term open label clinical trials with diabetic patients, pregabalin treatment did not appear to be associated with loss of glycemic control (as measured by HbA_{1C}).

Peripheral Edema

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

In controlled clinical trials the incidence of peripheral edema was 6% in the pregabalin group compared with 2% in the placebo group. In controlled clinical trials, 0.6% of pregabalin patients and no placebo patients withdrew due to peripheral edema.

Higher frequencies of weight gain and peripheral edema were observed in patients taking both LYRICA 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, care should be taken when co-administering LYRICA 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, LYRICA should be used with caution in these patients.

Creatine Kinase Elevations

Pregabalin treatment was associated with creatine kinase elevations. Mean changes in creatine kinase from baseline to the maximum value were 60 U/L for pregabalin-treated patients and 28 U/L for the placebo patients. In all controlled trials across multiple patient populations, 2% of patients on pregabalin and 1% of placebo patients had a value of creatine kinase at least three times the upper limit of normal. Three pregabalin treated subjects had events reported as rhabdomyolysis in premarketing clinical trials. The relationship between these myopathy events and pregabalin is not completely understood because the cases had documented factors that may have caused or contributed to these events. Prescribers should instruct patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if these muscle symptoms are accompanied by malaise or fever. Pregabalin treatment should be discontinued if myopathy is diagnosed or suspected or if markedly elevated creatine kinase levels occur.

Laboratory Changes

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, 2% of placebo patients and 3% of pregabalin patients experienced a potentially clinically significant decrease in platelets, defined as 20% below baseline value and <150 x 10^3/µL. In randomized controlled trials, pregabalin was not associated with an increase in bleeding related adverse events.

ECG Changes

PR Interval Prolongation

Pregabalin treatment was associated with mild PR interval prolongation. In analyses of clinical trial ECG data, the mean PR interval increase was 3-6 msec at pregabalin doses ≥300 mg/day. This mean change difference was not associated with an increased risk of PR increase ≥25% from baseline, an increased percentage of subjects with on-treatment PR >200 msec, or an increased risk of adverse events 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.

Information for Patients

Patients should be counseled that LYRICA may cause dizziness, somnolence, blurred vision and other CNS signs and symptoms. Accordingly, they should be advised not to drive, operate complex machinery, or engage in other hazardous activities until they have gained sufficient experience on pregabalin to gauge whether or not it affects their mental, visual, and/or motor performance adversely.

Patients should be counseled that LYRICA may cause visual disturbances. Patients should be informed that if changes in vision occur, they should notify their physician (see **PRECAUTIONS).**

Patients should be advised to take LYRICA as prescribed. Abrupt or rapid discontinuation may result in insomnia, nausea, headache, or diarrhea.

Patients should be counseled that LYRICA may cause edema and weight gain.

Patients should be advised that concomitant treatment with LYRICA and a thiazolidinedione antidiabetic agent may lead to an additive effect on edema and weight gain. For patients with preexisting cardiac conditions, this may increase the risk of heart failure.

Patients should be instructed to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

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

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

Patients should be instructed to notify their physician if they become pregnant or intend to become pregnant during therapy, and to notify their physician if they are breast feeding or intend to breast feed during therapy.

Men being treated with LYRICA who plan to father a child should be informed of the potential risk of male-mediated teratogenicity. In preclinical studies in rats, pregabalin was associated with an increased risk of male-mediated teratogenicity. The clinical significance of this finding is uncertain (see **PRECAUTIONS, Carcinogenesis and Impairment of Fertility).**

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

Patients should be informed of the availability of a patient information leaflet, and they should be instructed to read the leaflet prior to taking LYRICA.

Drug Interactions

Since pregabalin is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (<2% of a dose recovered in urine as metabolites), and does not bind to plasma proteins, its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions or

PRECAUTIONS *(continued)*

protein binding displacement. *In vitro* and *in vivo* studies showed that LYRICA is unlikely to be involved in significant pharmacokinetic drug interactions. Specifically, there are no pharmacokinetic interactions between pregabalin and the following antiepileptic drugs: carbamazepine, valproic acid, lamotrigine, phenytoin, phenobarbital, and topiramate. Important pharmacokinetic interactions would also not be expected to occur between pregabalin and commonly used antiepileptic drugs (see **CLINICAL PHARMACOLOGY).**

Pharmacodynamics

Multiple oral doses of pregabalin were co-administered with oxycodone, lorazepam, or ethanol. Although no pharmacokinetic interactions were seen, additive effects on cognitive and gross motor functioning were seen when pregabalin was co-administered with those drugs. No clinically important effects on respiration were seen (see **PRECAUTIONS, Dizziness and Somnolence** and **Information for Patients).**

Animal Toxicology

Dermatopathy

Skin lesions ranging from erythema to necrosis were seen in repeated-dose toxicology studies in both rats and monkeys. The etiology of these skin lesions is unknown. At the maximum recommended human dose (MRD) of 600 mg/day, there is a 2-fold safety margin for the dermatological lesions. The more severe dermatopathies involving necrosis were associated with pregabalin exposures (as expressed by plasma AUCs) of approximately 3 to 8 times those achieved in humans given the MRD. No increase in incidence of skin lesions was observed in clinical studies.

Ocular Lesions

Ocular lesions (characterized by retinal atrophy [including loss of photoreceptor cells] and/or corneal inflammation/mineralization) were observed in two lifetime carcinogenicity studies in Wistar rats. These findings were observed at plasma pregabalin exposures (AUC) ≥2 times those achieved in humans given the maximum recommended dose of 600 mg/day. A no-effect dose for ocular lesions was not established. Similar lesions were not observed in lifetime carcinogenicity studies in two strains of mice or in monkeys treated for 1 year.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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 effects 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.

Human Data

In a double-blind, placebo-controlled clinical trial to assess the effect of pregabalin on sperm motility, 30 healthy male subjects were exposed to pregabalin at a dose of 600 mg/day. After 3 months of treatment (one complete sperm cycle), the difference between placebo- and pregabalin-treated subjects in mean percent sperm with normal motility was <4% and neither group had a mean change from baseline of more than 2%. Effects on other male reproductive parameters in humans have not been adequately studied.

Pregnancy

Pregnancy Category C

Increased incidences of fetal structural abnormalities and other manifestations of developmental toxicity, including lethality, growth retardation, and nervous and reproductive system functional impairment, were observed in the offspring of rats and rabbits given pregabalin during pregnancy, at doses that produced plasma pregabalin exposures (AUC) ≥5 times human exposure at the maximum recommended dose (MRD) of 600 mg/day.

When pregnant rats were given pregabalin (500, 1250, or 2500 mg/kg) orally throughout the period of organogenesis, incidences of specific skull alterations attributed to abnormally advanced ossification (premature fusion of the jugal and nasal sutures) were increased at ≥1250 mg/kg, and incidences of skeletal variations and retarded ossification were increased at all doses. Fetal body weights were decreased at the highest dose. The low dose in this study was associated with a plasma exposure (AUC) approximately 17 times human exposure at the MRD of 600 mg/day. A no-effect dose for rat embryo-fetal developmental toxicity was not established.

When pregnant rabbits were given pregabalin (250, 500, or 1250 mg/kg) orally throughout the period of organogenesis, decreased fetal body weight and increased incidences of skeletal malformations, visceral variations, and retarded ossification were observed at the highest dose. The no-effect dose for developmental toxicity in rabbits (500 mg/kg) was associated with a plasma exposure approximately 16 times human exposure at the MRD.

In a study in which female rats were dosed with pregabalin (50, 100, 250, 1250, or 2500 mg/kg) throughout gestation and lactation, offspring growth was reduced at ≥ 100 mg/kg and offspring survival was decreased at ≥ 250 mg/kg. The effect on offspring survival was pronounced at doses ≥1250 mg/kg, with 100% mortality in high-dose litters. When offspring were tested as adults, neurobehavioral abnormalities (decreased auditory startle responding) were observed at ≥250 mg/kg and reproductive impairment (decreased fertility and litter size) was seen at 1250 mg/kg. The no-effect dose for pre- and postnatal developmental toxicity in rats (50 mg/kg) produced a plasma exposure approximately 2 times human exposure at the MRD.

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

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

Use in Nursing Mothers: It is not known if pregabalin is excreted in human milk; it is, however, present in the milk of rats. Because many drugs are excreted in human milk, and because of the potential for tumorigenicity shown for pregabalin in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

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

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

Geriatric Use

In controlled clinical studies of LYRICA in neuropathic pain associated with diabetic peripheral neuropathy, 306 patients were 65 to 74 years of age, and 88 patients were 75 years of age or older.

In controlled clinical studies of LYRICA in neuropathic pain associated with postherpetic neuralgia, 282 patients were 65 to 74 years of age, and 379 patients were 75 years of age or older.

In controlled clinical studies of LYRICA in epilepsy, there were only 10 patients 65 to 74 years of age, and 2 patients who were 75 years of age or older.

No overall differences in safety and efficacy were observed between these patients and younger patients. Even though the incidence of adverse events did not increase with age, greater sensitivity of some older individuals cannot be ruled out. LYRICA is known to be substantially excreted by the kidney, and the risk of toxic reactions to LYRICA may be greater in patients with impaired renal function.

Because LYRICA is eliminated primarily by renal excretion, the dose should be adjusted for elderly patients with renal impairment, as noted in the **DOSAGE AND ADMINISTRATION** section.

ADVERSE REACTIONS

In all controlled and uncontrolled trials across various patient populations during the premarketing development of pregabalin, more than 10,000 patients have received pregabalin. Approximately 5000 patients were treated for 6 months or more, over 3100 patients were treated for 1 year or longer, and over 1400 patients were treated for at least 2 years.

Adverse Events Most Commonly Leading to Discontinuation in All Controlled Clinical Studies

In controlled trials of all populations combined, 14% of patients treated with pregabalin and 7% of patients treated with placebo discontinued prematurely due to adverse events. In the pregabalin treatment group, the adverse events most frequently leading to discontinuation were dizziness (4%) and somnolence (3%). In the placebo group, 1% of patients withdrew due to dizziness and <1% withdrew due to somnolence. Other adverse events that led to discontinuation from controlled trials more frequently in the pregabalin group compared to the placebo group were ataxia, confusion, asthenia, thinking abnormal, blurred vision, incoordination, and peripheral edema (1% each).

Most Common Adverse Events in All Controlled Clinical Studies

In controlled trials of all patient populations combined, dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, and "thinking abnormal" (primarily difficulty with concentration/attention) were more commonly reported by subjects treated with pregabalin than by subjects treated with placebo (≥5% and twice the rate of that seen in placebo).

Controlled Studies with Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

Adverse Events Leading to Discontinuation

In clinical trials in patients with neuropathic pain associated with diabetic peripheral neuropathy, 9% of patients treated with pregabalin and 4% of patients treated with placebo discontinued prematurely due to adverse events. In the pregabalin treatment group, the most common reasons for discontinuation due to adverse events were dizziness (3%) and somnolence (2%). In comparison, <1% of placebo patients withdrew due to dizziness and somnolence. Other reasons for discontinuation from the trials, occurring with greater frequency in the pregabalin group than in the placebo group, were asthenia, confusion, and peripheral edema. Each of these events led to withdrawal in approximately 1% of patients.

Most Common Adverse Events

Table 2 lists all adverse events, regardless of causality, occurring in ≥1% of patients with neuropathic pain associated with diabetic neuropathy in the combined pregabalin group for which the incidence was greater in this combined pregabalin group than in the placebo group. A majority of pregabalin-treated patients in clinical studies had adverse events with a maximum intensity of "mild" or "moderate".

Table 2. Treatment-emergent adverse event incidence in controlled trials in Neuropathic Pain Associated with Diabetic Peripheral Neuropathy (Events in at least 1% of all LYRICA-treated patients and at least numerically more in all pregabalin than in the placebo group)

Body system - Preferred term	75 mg/day [N=77] %	150 mg/day [N=212] %	300 mg/day [N=321] %	600 mg/day [N=369] %	All PGB* [N=979] %	Placebo [N=459] %
Body as a whole						
Asthenia	4	2	4	7	5	2
Accidental injury	5	2	2	6	4	3
Back pain	0	2	1	2	2	0
Chest pain	4	1	1	2	2	1
Face edema	0	1	1	2	1	0
Digestive system						
Dry mouth	3	2	5	7	5	1
Constipation	0	2	4	6	4	2
Flatulence	3	0	2	3	2	1
Metabolic and nutritional disorders						
Peripheral edema	4	6	9	12	9	2
Weight gain	0	4	4	6	4	0
Edema	0	2	4	2	2	0
Hypoglycemia	1	3	2	1	2	1
Nervous system						
Dizziness	8	9	23	29	21	5
Somnolence	4	6	13	16	12	3
Neuropathy	9	2	2	5	4	3
Ataxia	6	1	2	4	3	1
Vertigo	1	2	2	4	3	1
Confusion	0	1	2	3	2	1
Euphoria	0	0	3	2	2	0
Incoordination	1	0	2	2	2	0
Thinking abnormal[a]	1	0	1	3	2	0
Tremor	1	1	1	2	1	0
Abnormal gait	1	0	1	3	1	0
Amnesia	3	1	0	2	1	0
Nervousness	0	1	1	1	1	0
Respiratory system						
Dyspnea	3	0	2	2	2	1
Special senses						
Blurry vision[b]	3	1	3	6	4	2
Abnormal vision	1	0	1	1	1	0

*PGB: pregabalin

[a] Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slowed thinking.

[b] Investigator term; summary level term is amblyopia

Controlled Studies in Postherpetic Neuralgia

Adverse Events Leading to Discontinuation

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

Most Common Adverse Events

Table 3 lists all adverse events, regardless of causality, occurring in ≥ 1% of patients with neuropathic pain associated with postherpetic neuralgia in the combined pregabalin group for which the incidence was greater in this combined pregabalin group than in the placebo group. In addition, an event is included, even if the incidence in the all pregabalin group is not greater than in the placebo group, if the incidence of the event in the 600 mg/day group is more than twice that in the placebo group. A majority of pregabalin-treated patients in clinical studies had adverse events with a maximum intensity of "mild" or "moderate".

Table 3. Treatment-emergent adverse event incidence in controlled trials in Neuropathic Pain Associated with Postherpetic Neuralgia (Events in at least 1% of all LYRICA-treated patients and at least numerically more in all pregabalin than in the placebo group)

Body system - Preferred term	75 mg/d [N=84] %	150 mg/d [N=302] %	300 mg/d [N=312] %	600 mg/d [N=154] %	All PGB* [N=852] %	Placebo [N=398] %
Body as a whole						
Infection	14	8	6	3	7	4
Headache	5	9	5	8	7	5
Pain	5	4	5	5	5	4
Accidental injury	4	3	3	5	3	2
Flu syndrome	1	2	2	1	2	1
Face edema	0	2	1	3	2	1
Digestive system						
Dry mouth	7	7	6	15	8	3
Constipation	4	5	5	5	5	2
Flatulence	2	1	2	3	2	1
Vomiting	1	1	3	3	2	1
Metabolic and nutritional disorders						
Peripheral edema	0	8	16	16	12	4
Weight gain	1	2	5	7	4	0
Edema	0	1	2	6	2	1
Musculoskeletal system						
Myasthenia	1	1	1	1	1	0
Nervous system						
Dizziness	11	18	31	37	26	9
Somnolence	8	12	18	25	16	5
Ataxia	1	2	5	9	5	1
Abnormal gait	0	2	4	8	4	1
Confusion	1	2	3	7	3	0
Thinking abnormal[a]	0	2	1	6	2	2
Incoordination	2	2	1	3	2	0
Amnesia	0	1	1	4	2	0
Speech disorder	0	0	1	3	1	0
Respiratory system						
Bronchitis	0	1	1	3	1	1
Special senses						
Blurry vision[b]	1	5	5	9	5	3
Diplopia	0	2	2	4	2	0
Abnormal vision	0	1	2	5	2	0
Eye Disorder	0	1	1	2	1	0
Urogenital System						
Urinary Incontinence	0	1	1	2	1	0

*PGB: pregabalin

[a] Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slowed thinking.

[b] Investigator term; summary level term is amblyopia

Controlled Add-On Studies in Epilepsy

Adverse Events Leading to Discontinuation

Approximately 15% of patients receiving pregabalin and 6% of patients receiving placebo in add-on epilepsy trials discontinued prematurely due to adverse events. In the pregabalin treatment group, the adverse events most frequently leading to discontinuation were dizziness (6%), ataxia (4%), and somnolence (3%). In comparison, <1% of patients in the placebo group withdrew due to each of these events. Other adverse events that led to discontinuation of at least 1% of patients in the pregabalin group and at least twice as frequently compared to the placebo group were asthenia, diplopia, blurred vision, thinking abnormal, nausea, tremor, vertigo, headache, and confusion (which each led to withdrawal in 2% or less of patients).

Most Common Adverse Events

Table 4 lists all dose-related adverse events, regardless of causality, occurring in at least 2% of all LYRICA-treated patients. Dose-relatedness was defined as the incidence of the adverse event in the 600 mg/day group was at least 2% greater than the rate in both the placebo and 150 mg/day groups. In these studies, 758 patients received pregabalin and 294 patients received placebo for up to 12 weeks. Because patients were also treated with 1 to 3 other AEDs, it is not possible to determine whether the following adverse events can be ascribed to pregabalin alone, or the combination of pregabalin and other AEDs. A majority of pregabalin-treated patients in these studies had adverse events with a maximum intensity of "mild" or "moderate".

ADVERSE REACTIONS *(continued)*

Table 4. Dose-related treatment-emergent adverse event incidence in controlled trials in Epilepsy (Events in at least 2% of all LYRICA-treated patients and the adverse event in the 600 mg/day group was ≥2% the rate in both the placebo and 150 mg/day groups

Body System - Preferred Term	150 mg/d [N = 185] %	300 mg/d [N = 90] %	600 mg/d [N = 395] %	All PGB* [N = 670][a] %	Placebo [N = 294] %
Body as a Whole					
Accidental Injury	7	11	10	9	5
Pain	3	2	5	4	3
Digestive System					
Increased Appetite	2	3	6	5	1
Dry Mouth	1	2	6	4	1
Constipation	1	1	7	4	2
Metabolic and Nutritional Disorders					
Weight Gain	5	7	16	12	1
Peripheral Edema	3	3	6	5	2
Nervous System					
Dizziness	18	31	38	32	11
Somnolence	11	18	28	22	11
Ataxia	6	10	20	15	4
Tremor	3	7	11	8	4
Thinking Abnormal[b]	4	8	9	8	2
Amnesia	3	2	6	5	2
Speech Disorder	1	2	7	5	1
Incoordination	1	3	6	4	1
Abnormal Gait	1	3	5	4	0
Twitching	0	4	5	4	1
Confusion	1	2	5	4	2
Myoclonus	1	0	4	2	0
Special Senses					
Blurred Vision[c]	5	8	12	10	4
Diplopia	5	7	12	9	4
Abnormal Vision	3	1	5	4	1

*PGB: pregabalin

[a] Excludes patients who received the 50 mg dose in Study E1.

[b] Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slowed thinking.

[c] Investigator term; summary level term is amblyopia.

Adverse events occurring in ≥ 2% of patients with partial onset seizures in the combined pregabalin group for which the incidence was greater in this combined pregabalin group than in the placebo group, but did not show dose-relatedness, include the following: asthenia, infection, chest pain, vomiting, nervousness, nystagmus, paresthesias, visual field defect.

Other Adverse Events Observed During the Clinical Studies of LYRICA (pregabalin)

Following is a list of treatment-emergent adverse events reported by patients treated with LYRICA during all clinical trials. The listing does not include those events already listed in the previous tables or elsewhere in labeling, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening.

Events are categorized by body system and listed in order of decreasing frequency according to the following definitions: **frequent** adverse events are those occurring on one or more occasions in at least 1/100 patients; **infrequent** adverse events are those occurring in 1/100 to 1/1000 patients; **rare** events are those occurring in fewer than 1/1000 patients. Events of major clinical importance are described in the **WARNINGS** and **PRECAUTIONS** sections.

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

Cardiovascular System – *Infrequent:* Deep thrombophlebitis, Heart failure, Hypotension, Postural hypotension, Retinal vascular disorder, Syncope; *Rare:* ST Depressed, Ventricular Fibrillation

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

Hemic and Lymphatic System – *Frequent:* Ecchymosis; *Infrequent:* Anemia, Eosinophilia, Hypochromic anemia, Leukocytosis, Leukopenia, Lymphadenopathy, Thrombocytopenia; *Rare:* Myelofibrosis, Polycythemia, Prothrombin decreased, Purpura, Thrombocythemia

Metabolic and Nutritional Disorders – *Rare:* Glucose Tolerance Decreased, Urate Crystalluria

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

Nervous System – *Frequent:* Anxiety, Depersonalization, Hypertonia, Hypesthesia, Libido decreased, Nystagmus, Paresthesia, Stupor, Twitching; *Infrequent:* 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 Barre syndrome, Hypalgesia, Intracranial hypertension, Manic reaction, Paranoid reaction, Peripheral neuritis, Psychotic depression, Schizophrenic reaction, Torticollis, Trismus

Respiratory System – *Rare:* Apnea, Atelectasis, Bronchiolitis, Hiccup, Laryngismus, Lung edema, Lung fibrosis, Yawn

Skin and Appendages – *Frequent:* Pruritus, *Infrequent:* Alopecia, Dry skin, Eczema, Hirsutism, Skin ulcer, Urticaria, Vesiculobullous rash; *Rare:* Angioedema, Exfoliative dermatitis, Lichenoid dermatitis, Melanosis, Petechial rash, Purpuric rash, Pustular rash, Skin atrophy, Skin necrosis, Skin nodule, Stevens-Johnson syndrome, Subcutaneous nodule

Special senses – *Frequent:* Conjunctivitis, Diplopia, Otitis media, Tinnitus; *Infrequent:* Abnormality of accommodation, Blepharitis, Dry eyes, Eye hemorrhage, Hyperacusis, Photophobia, Retinal edema, Taste loss, Taste perversion; *Rare:* Anisocoria, Blindness, Corneal ulcer, Exophthalmos, Extraocular palsy, Iritis, Keratitis, Keratoconjunctivitis, Miosis, Mydriasis, Night blindness, Ophthalmoplegia, Optic atrophy, Papilledema, Parosmia, Ptosis, Uveitis

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

Comparison of Gender and Race

The overall adverse event profile of pregabalin was similar between women and men. There are insufficient data to support a statement regarding the distribution of adverse experience reports by race.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: LYRICA is a Schedule V controlled substance.

In a study of recreational users (N=15) of sedative/hypnotic drugs, including alcohol, Lyrica (450 mg, single dose) received subjective ratings of "good drug effect," "high" and "liking" to a degree that was similar to diazepam (30 mg, single dose). In controlled clinical studies in over 5500 patients, 4% of Lyrica-treated patients and 1% of placebo-treated patients overall reported euphoria as an adverse event, though in some patient populations studied, this reporting rate was higher and ranged from 1 to 12%. In clinical studies, following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache or diarrhea (see **PRECAUTIONS**, Abrupt Discontinuation), suggestive of physical dependence.

Pregabalin is not known to be active at receptor sites associated with drugs of abuse. As with any CNS active drug, physicians should carefully evaluate patients for history of drug abuse and observe them for signs of LYRICA misuse or abuse (e.g., development of tolerance, dose escalation, drug-seeking behavior).

OVERDOSAGE

Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans

There is limited experience with overdose of pregabalin. The highest reported accidental overdose of pregabalin during the clinical development program was 8000 mg, and there were no notable clinical consequences. In clinical studies, some patients took as much as 2400 mg/day. The types of adverse events experienced by patients exposed to higher doses (≥900 mg) were not clinically different from those of patients administered recommended doses of pregabalin.

Treatment or Management of Overdose

There is no specific antidote for overdose with pregabalin. If indicated, elimination of unabsorbed drug may be attempted by emesis or gastric lavage; usual precautions should be observed to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient. A Certified Poison Control Center should be contacted for up-to-date information on the management of overdose with pregabalin.

Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment. Standard hemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours).

DOSAGE AND ADMINISTRATION

LYRICA® is given orally with or without food.

Neuropathic pain associated with diabetic peripheral neuropathy

The maximum recommended dose of LYRICA is 100 mg three times a day (300 mg/day) in patients with creatinine clearance of at least 60 mL/min. Dosing should begin at 50 mg three times a day (150 mg/day) and may be increased to 300 mg/day within 1 week based on efficacy and tolerability. Because LYRICA is eliminated primarily by renal excretion, the dose should be adjusted for patients with reduced renal function (see **Patients with Renal Impairment).**

Although LYRICA 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 effects, treatment with doses above 300 mg/day are not recommended (see **ADVERSE REACTIONS).**

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

Postherpetic neuralgia

The recommended dose of LYRICA 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. Dosing should begin at 75 mg two times a day, or 50 mg three times a day (150 mg/day) and may be increased to 300 mg/day within 1 week based on efficacy and tolerability. Because LYRICA is eliminated primarily by renal excretion, the dose should be adjusted for patients with reduced renal function (see **Patients with Renal Impairment).**

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 LYRICA, 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 effects and the higher rate of treatment discontinuation due to adverse events, dosing above 300 mg/day should be reserved only for those patients who have on-going pain and are tolerating 300 mg daily (see **ADVERSE REACTIONS).**

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

Epilepsy

LYRICA at doses of 150 to 600 mg/day has been shown to be effective as adjunctive therapy in the treatment of partial onset seizures in adults. The total daily dose should be divided and given either two or three times daily. Both the efficacy and adverse event profiles of LYRICA have been shown to be dose-related. 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.

The effect of dose escalation rate on the tolerability of LYRICA has not been formally studied.

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

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

Patients with Renal Impairment

In view of dose-dependent adverse events and since LYRICA is eliminated primarily by renal excretion, the dose should be adjusted in patients with reduced renal function. Dosage adjustment in patients with renal impairment should be based on CLcr, as indicated in Table 5. 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:

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

For patients undergoing hemodialysis, pregabalin daily dose should be adjusted based on renal function. In addition to the daily dose adjustment, a supplemental dose should be given immediately following every 4-hour hemodialysis treatment (see Table 5).

Table 5: Pregabalin Dosage Adjustment Based on Renal Function

Creatinine Clearance (CLcr) (mL/min)	Total Pregabalin Daily Dose (mg/day)[a]			Dose Regimen
≥60	150	300	600	BID or TID
30-60	75	150	300	BID or TID
15-30	25-50	75	150	QD or BID
<15	25	25-50	75	QD
Supplementary dosage following hemodialysis (mg)[b]				
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 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.

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

[b] Supplementary dose is a single additional dose.

HOW SUPPLIED

25-mg capsules:
White, hard-gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 25" on the body; available in:
Bottles of 90: NDC 0071-1012-68

50-mg capsules:
White, hard-gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 50" and an ink band on the body, available in:
Bottles of 90: NDC 0071-1013-68

75-mg capsules:
White/orange, hard-gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 75" on the body; available in:
Bottles of 90: NDC 0071-1014-68

100-mg capsules:
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Bottles of 90: NDC 0071-1015-68

150-mg capsules:
White, hard-gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 150" on the body, available in:
Bottles of 90: NDC 0071-1016-68

200-mg capsules:
Light orange, hard-gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 200" on the body, available in:
Bottles of 90: NDC 0071-1017-68

225-mg capsules:
White/light orange, hard-gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 225" on the body; available in:
Bottles of 90: NDC 0071-1019-68

300-mg capsules:
White/orange, hard-gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 300" on the body, available in:
Bottles of 90: NDC 0071-1018-68

Storage

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

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LAB-0294-4
70-6146-00-1

Revised August 2005

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23-6167-00-0

LYRICA® PREGABALIN CV capsules

PATIENT INFORMATION

(LEER-i-kah)

Read the Patient Information that comes with LYRICA before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your condition or treatment. If you have any questions about LYRICA, ask your doctor or pharmacist.

What is the most important information I should know about LYRICA?

1. **LYRICA may cause dizziness and sleepiness.**
   - **Do not drive a car, work with machines, or do other dangerous activities until you know how LYRICA affects how alert you are. Ask your doctor when it is okay to do these activities.**
2. **LYRICA may cause problems with your eyesight, including blurry vision.**
   - **Call your doctor if you have any changes in your eyesight.**

What is LYRICA?

LYRICA is a prescription medicine used in adults, 18 years and older, to treat:

- pain from damaged nerves (neuropathic pain) that happens with diabetes
- pain from damaged nerves (neuropathic pain) that follows healing of shingles (a painful rash that comes after a herpes zoster infection)
- partial seizures when taken together with other seizure medicines

Pain From Damaged Nerves (neuropathic pain)

Diabetes and shingles can damage your nerves. Pain from damaged nerves may feel sharp, burning, tingling, shooting, or numb. If you have diabetes, the pain can be in your arms, hands, fingers, legs, feet, or toes. If you have shingles, the pain is in the area of your rash. You may experience this kind of pain even with a very light touch. LYRICA can help relieve the pain. Some people taking LYRICA had less pain by the end of the first week of LYRICA therapy. LYRICA may not work for everyone. LYRICA has not been studied for nerve pain in children under 18 years of age.

Partial Seizures

Partial seizures start in one part of the brain. A seizure can make you fearful, confused, or just feel “funny”. You may smell strange smells. A seizure may cause your arm or leg to jerk or shake. It can spread to other parts of your brain, make you pass out, and cause your whole body to start jerking.

LYRICA can lower the number of seizures for people who are already taking seizure medicine. LYRICA has not been studied for partial seizures in children under 18 years of age.

Who Should Not Take LYRICA?

Do not take LYRICA if you are allergic to any of its ingredients. The active ingredient is pregabalin. See the end of this leaflet for a complete list of ingredients in LYRICA.

What should I tell my doctor before taking LYRICA?

Tell your doctor about all your medical conditions, including if you:

- **have any kidney problems or get kidney dialysis**
- **have heart problems including heart failure**
- **have a bleeding problem or a low blood platelet count**
- **are pregnant or plan to become pregnant.** It is not known if LYRICA may harm your unborn baby. You and your doctor will have to decide if LYRICA is right for you while you are pregnant.
- **are breastfeeding.** It is not known if LYRICA passes into breast milk and if it can harm your baby. You and your doctor should decide whether you should take LYRICA or breastfeed, but not both.

Tell your doctor about all the medicines you take including prescription or non-prescription medicines, vitamins or herbal supplements. LYRICA and other medicines may affect each other. Especially tell your doctor if you take:

- rosiglitazone (Avandia®) or pioglitazone (Actos®) for diabetes. You may have a higher chance of weight gain or swelling if these medicines are taken with LYRICA. See "What are the possible side effects of LYRICA?"
- any narcotic pain medicine (such as oxycodone), tranquilizers or medicines for anxiety (such as lorazepam). You may have a higher chance for dizziness and sleepiness if these medicines are taken with LYRICA. See "What is the most important information I should know about LYRICA?"
- any medicines that make you sleepy

Know all the medicines you take. Keep a list of them with you to show your doctor and pharmacist each time you get a new medicine.

Tell your doctor if you plan to father a child. Animal studies showed that pregabalin, the active ingredient in LYRICA, made male animals less fertile. Also, in animal studies, birth defects occurred in the offspring of male animals who were treated with pregabalin. It is not known if these effects would happen in people.

How should I take LYRICA?

- Take LYRICA exactly as prescribed. Your doctor may adjust your dose during treatment. Do not change your dose without talking to your doctor.
- Do not stop taking LYRICA suddenly without talking to your doctor. If you stop taking LYRICA suddenly, you may have headaches, nausea, diarrhea or trouble sleeping. Talk with your doctor about how to slowly stop LYRICA.
- LYRICA is usually taken 2 or 3 times a day, depending on your medical condition. Your doctor will tell you how much LYRICA to take and when to take it. Take LYRICA at the same times each day.

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- LYRICA may be taken with or without food.
- If you miss a dose by a few hours, take it as soon as you remember. If it is close to your next dose, just take LYRICA at your next regular time. **Do not** take two doses at the same time.
- If you take too much LYRICA, call your doctor or poison control center or go to the nearest emergency room right away.

What Should I Avoid While Taking LYRICA?

- **Do not drive a car, work with machines, or do other dangerous activities until you know how LYRICA affects how alert you are.** See "What is the most important information I should know about LYRICA?"
- **Do not drink alcohol while taking LYRICA.** LYRICA and alcohol can affect each other and increase side effects such as sleepiness and dizziness. This can be dangerous.

Do not take other medicines without talking to your doctor. Other medicines include prescription and non-prescription medicines, vitamins, and herbal supplements. LYRICA and other medicines may affect each other and increase the side effects of sleepiness and dizziness. Be especially careful about medicines that make you sleepy (such as sleeping pills, anxiety medicines, tranquilizers and some antihistamines, pain relievers and seizure medicines).

What are the possible side effects of LYRICA?

LYRICA may cause side effects including:

- **dizziness and sleepiness.** See "What is the most important information I should know about LYRICA?"
- **eyesight problems.** See "What is the most important information I should know about LYRICA?"
- **weight gain and swelling of the hands and feet (edema).** Weight gain may affect the management of diabetes. Weight gain and swelling can also be a serious problem for people with heart problems.
- **unexplained muscle problems, such as muscle pain, soreness, or weakness.** If you develop these symptoms, especially if you also feel sick and have a fever, tell your doctor right away.

The most common side effects of LYRICA are:

- dizziness
- blurry vision
- weight gain
- sleepiness
- trouble concentrating
- swelling of hands and feet
- dry mouth

LYRICA caused skin sores in animals. Although skin sores were not seen in studies in people, if you have diabetes, you should pay extra attention to your skin while taking LYRICA and tell your doctor of any sores or skin problems.

LYRICA may cause some people to feel "high." Tell your doctor, if you have abused prescription medicines, street drugs, or alcohol in the past.

Tell your doctor about any side effect that bothers you or that does not go away.

These are not all the side effects of LYRICA. For more information, ask your doctor or pharmacist.

How should I store LYRICA?

- Store LYRICA at room temperature, 59 to 86°F (15 to 30°C) in its original package.
- Safely throw away LYRICA that is out of date or no longer needed.
- **Keep LYRICA and all medicines out of the reach of children.**

General information about LYRICA

Medicines are sometimes prescribed for conditions other than those listed in patient information leaflets. Do not use LYRICA for a condition for which it was not prescribed. Do not give LYRICA to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about LYRICA. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about LYRICA that is written for health professionals.
You can also visit the LYRICA website at www.LYRICA.com or call 1-866-4LYRICA.

What are the ingredients In LYRICA?

Active ingredient: pregabalin
Inactive ingredients: lactose monohydrate, cornstarch, talc; **Capsule shell:** gelatin and titanium dioxide; Orange capsule shell: red iron oxide; White capsule shell: sodium lauryl sulfate, colloidal silicon dioxide. Colloidal silicon dioxide is a manufacturing aid that may or may not be present in the capsule shells.
Imprinting ink: shellac, black iron oxide, propylene glycol, potassium hydroxide.

Pfizer
Parke-Davis
Division of Pfizer Inc, NY, NY 10017

23-6167-00-0

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

DOSAGE AND USE
See accompanying prescribing information.

Each capsule contains 50 mg pregabalin.

Manufactured by:
Pfizer Pharmaceuticals LLC
Vega Baja, PR 00694

PROFESSIONAL SAMPLE – NOT FOR SALE
30 Capsules NDC 63539-013-30

LYRICA™ CV
PREGABALIN
capsules
50 mg

Distributed by
U.S. Pharmaceuticals
Pfizer Inc, NY, NY 10017

Rx only

54-6261-32-0

[redacted]

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

DOSAGE AND USE
See accompanying prescribing information.

Each capsule contains 75 mg pregabalin.

Manufactured by:
Pfizer Pharmaceuticals LLC
Vega Baja, PR 00694

PROFESSIONAL SAMPLE – NOT FOR SALE
30 Capsules NDC 63539-014-30

LYRICA™ CV
PREGABALIN
capsules
75 mg

Distributed by
U.S. Pharmaceuticals
Pfizer Inc, NY, NY 10017

Rx only

54-6258-32-0

[redacted]

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

DOSAGE AND USE
See accompanying prescribing information.

Each capsule contains 50 mg pregabalin.

Manufactured by:
Pfizer Pharmaceuticals LLC
Vega Baja, PR 00694

PROFESSIONAL SAMPLE – NOT FOR SALE
45 Capsules NDC 63539-013-47

LYRICA™ PREGABALIN CV
50 mg *capsules*

Distributed by
U.S. Pharmaceuticals
Pfizer Inc, NY, NY 10017

Rx only

54-6257-32-0

[redacted]

TOP

LYRICA™ PREGABALIN Cv capsules

50 mg

12 Bottles x 30 Capsules

Your Pfizer representative is:

PROFESSIONAL SAMPLE – NOT FOR SALE
NDC 63539-013-30
Rx only

Please call for additional samples or information.

LYRICA™ PREGABALIN Cv capsules

50 mg

12 Bottles x 30 Capsules

NDC 63539-013-30
Rx only

PROFESSIONAL SAMPLE – NOT FOR SALE

LYRICA™ PREGABALIN Cv capsules

50 mg

12 Bottles x 30 Capsules

LYRICA™ PREGABALIN Cv capsules

50 mg

12 Bottles x 30 Capsules

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

DOSAGE AND USE
See accompanying prescribing information.

Each capsule contains 50 mg pregabalin.

See bottom panel for lot number and expiration date.

Manufactured by:
Pfizer Pharmaceuticals LLC
Vega Baja, PR 00694

Distributed by
U.S. Pharmaceuticals
Pfizer Inc, NY, NY 10017

LYRICA™ PREGABALIN Cv capsules

50 mg

15-6261-00-0
873

FPO: ITF 30% x 20mm
0156261000

PRINTED SIDE

LYRICA™ PREGABALIN capsules CV

75 mg

50 mg

Early Experience Kit Contains:
5 Bottles (50 mg x 45 Capsules) NDC 63539-013-47
5 Bottles (75 mg x 30 Capsules) NDC 63539-014-30

LYRICA™ PREGABALIN capsules CV

75 mg

50 mg

Rx only

PROFESSIONAL SAMPLE–NOT FOR SALE

#920

75 mg

LYRICA™ PREGABALIN capsules CV

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

DOSAGE AND USE
See accompanying prescribing information.

Each 50 mg capsule contains 50 mg pregabalin.
Each 75 mg capsule contains 75 mg pregabalin.

See bottom panel for lot number and expiration date.

Manufactured by:
Pfizer Pharmaceuticals LLC
Vega Baja, PR 00694

Distributed by
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Pfizer Inc, NY, NY 10017

50 mg

15-6260-00-0

FPO: ITV 20mm x 30%
15626000

NON VARNISH AREA

Rx only

LYRICA™ PREGABALIN capsules CV

75 mg

50 mg

PROFESSIONAL SAMPLE–NOT FOR SALE

Early Experience Kit Contains:
5 Bottles (50 mg x 45 Capsules) NDC 63539-013-47
5 Bottles (75 mg x 30 Capsules) NDC 63539-014-30

Please see full prescribing information.

75 mg

LYRICA™ PREGABALIN capsules CV

50 mg

50 mg

LYRICA™ PREGABALIN capsules CV

75 mg

TOP

FITS ON FT

LYRICA™ CV
PREGABALIN
capsules

75mg

12 Bottles x 30 Capsules

15-6258-00-0
873

LYRICA™ CV
PREGABALIN
capsules

NDC 63539-014-30
Rx only

PROFESSIONAL SAMPLE - NOT FOR SALE

12 Bottles x 30 Capsules

75mg

LYRICA™ CV
PREGABALIN
capsules

75mg

12 Bottles x 30 Capsules

FPO- ITF 30% x 20mm
0156258000

LYRICA™ CV
PREGABALIN
capsules

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

DOSAGE AND USE
See accompanying prescribing information.

Each capsule contains 75 mg pregabalin.

See bottom panel for lot number and expiration date.

Manufactured by:
Pfizer Pharmaceuticals LLC
Vega Baja, PR 00694

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Pfizer Inc, NY, NY 10017

75mg

PRINTED SIDE

LYRICA™ CV
PREGABALIN
capsules
75 mg

Early Experience Kit Contains:
10 Bottles (75 mg x 30 Capsules) NDC 63539-014-30

LYRICA™ CV
PREGABALIN
capsules
75 mg

Rx only
PROFESSIONAL SAMPLE–NOT FOR SALE

#920

LYRICA™ CV
PREGABALIN
capsules

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

DOSAGE AND USE
See accompanying prescribing information.

Each capsule contains 75 mg pregabalin.

See bottom panel for lot number and expiration date.

Manufactured by:
Pfizer Pharmaceuticals LLC
Vega Baja, PR 00694

Distributed by
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75 mg

15-6176-00-0

FPO: ITV 20mm x 30%
15617600

NON VARNISH AREA

Rx only
75 mg
LYRICA™ CV
PREGABALIN
capsules
PROFESSIONAL SAMPLE–NOT FOR SALE
Early Experience Kit Contains:
10 Bottles (75 mg x 30 Capsules) NDC 63539-014-30

Please see full prescribing information.

LYRICA™ CV
PREGABALIN
capsules
75 mg

LYRICA™ CV
PREGABALIN
capsules
75 mg

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Dispense in tight containers (USP).

DOSAGE AND USE
See accompanying prescribing information.

Each capsule contains 300 mg pregabalin.

Manufactured by:
Pfizer Pharmaceuticals LLC
Vega Baja, PR 00694

NDC 0071-1018-68

90 Capsules **Rx only**

Lyrica™ 300 C V
(pregabalin) capsules

300 mg

Distributed by
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FPO (100% x 12.25mm)
N 3 0071-1018-68 5

0582

05-6349-32-0

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Dispense in tight containers (USP).

DOSAGE AND USE
See accompanying prescribing information.

Each capsule contains 225 mg pregabalin.

Manufactured by:
Pfizer Pharmaceuticals LLC
Vega Baja, PR 00694

90 Capsules

NDC 0071-1019-68
Rx only

Lyrica™ 225 C V
(pregabalin) capsules

225 mg

Distributed by
Pfizer
Parke-Davis
Division of Pfizer Inc, NY, NY 10017

FPD (80% x 11.5mm)
N 3 0071-1019-68 2

0581

05-6269-32-0

[redacted]

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Dispense in tight containers (USP).

DOSAGE AND USE
See accompanying prescribing information.

Each capsule contains 200 mg pregabalin.

Manufactured by:
Pfizer Pharmaceuticals LLC
Vega Baja, PR 00694

90 Capsules

NDC 0071-1017-68
Rx only

Lyrica™ 200
(pregabalin) capsules
C-V

200 mg

Distributed by
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Division of Pfizer Inc, NY, NY 10017

FPD (80% x 11.5mm)
N 3 0071-1017-68 8

0580

05-6268-32-0

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Dispense in tight containers (USP).

DOSAGE AND USE
See accompanying prescribing information.

Each capsule contains 150 mg pregabalin.

Manufactured by:
Pfizer Pharmaceuticals LLC
Vega Baja, PR 00694

90 Capsules

NDC 0071-1016-68
Rx only

Lyrica™ 150
(pregabalin) capsules
C-V

150 mg

Distributed by
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Parke-Davis
Division of Pfizer Inc, NY, NY 10017

FPO (80% x 11.5mm)
N 3 0071-1016-68 1

0579

05-6267-32-0

[redacted]

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Dispense in tight containers (USP).

DOSAGE AND USE
See accompanying prescribing information.

Each capsule contains 100 mg pregabalin.

Manufactured by:
Pfizer Pharmaceuticals LLC
Vega Baja, PR 00694

NDC 0071-1015-68

90 Capsules **Rx only**

Lyrica™ 100
(pregabalin) capsules
C-V

100 mg

Distributed by
Pfizer
Parke-Davis
Division of Pfizer Inc, NY, NY 10017

FPO (80% x 5.5mm)
N3 0071-1015-68 4

0578

05-6266-32-0

[redacted]

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Dispense in tight containers (USP).

DOSAGE AND USE
See accompanying prescribing information.

Each capsule contains 75 mg pregabalin.

Manufactured by:
Pfizer Pharmaceuticals LLC
Vega Baja, PR 00694

NDC 0071-1014-68

90 Capsules **Rx only**

Lyrica™ 75
(pregabalin) capsules
C-V

75 mg

Distributed by
Pfizer
Parke-Davis
Division of Pfizer Inc, NY, NY 10017

FPO (80% x 5.5mm)
N3 0071-1014-68 7

0577

05-6265-32-0

[redacted]

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Dispense in tight containers (USP).

DOSAGE AND USE
See accompanying prescribing information.

Each capsule contains 50 mg pregabalin.

Manufactured by:
Pfizer Pharmaceuticals LLC
Vega Baja, PR 00694

NDC 0071-1013-68

90 Capsules **Rx only**

Lyrica™ 50 C V
(pregabalin) capsules

50 mg

Distributed by
Pfizer
Parke-Davis
Division of Pfizer Inc, NY, NY 10017

FPO (80% x 5.5mm)
N3 0071-1013-68 0

0576

05-6264-32-0

[redacted]

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Dispense in tight containers (USP).

DOSAGE AND USE
See accompanying prescribing information.

Each capsule contains 25 mg pregabalin.

Manufactured by:
Pfizer Pharmaceuticals LLC
Vega Baja, PR 00694

NDC 0071-1012-68

90 Capsules **Rx only**

Lyrica™ 25
(pregabalin) capsules
C V

25 mg

Distributed by
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Parke-Davis
Division of Pfizer Inc, NY, NY 10017

FPO (80% x 5.5mm)
N3 0071-1012-68 3

0575

05-6263-32-0

[redacted]