LACPRIL

(PREGABALIN)

لیک پرل کیپسولز

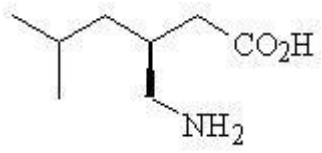
(پری گیبلین)

۵۰ ملی گرام، ۷۵ ملی گرام، ۱۰۰ ملی گرام،
۱۵۰ ملی گرام اور ۳۰۰ ملی گرام کیپسولز

50mg, 75mg, 100mg, 150mg & 300mg Capsules

DESCRIPTION

Pregabalin is described chemically as (*S*)-3-(aminomethyl)-5-methyl hexanoic 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.

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

LACPRIL (pregabalin) oral solution, 20 mg/mL, is administered orally and is supplied as a clear, colorless solution contained in a 16 fluid ounce white HDPE bottle with a polyethylene-lined closure. The oral solution contains 20 mg/mL of pregabalin, along with methylparaben, propylparaben, monobasic sodium phosphate anhydrous, dibasic sodium phosphate anhydrous, sucralose, artificial strawberry #11545 and purified water as inactive ingredients.

COMPOSITION:

LACPRIL 50mg Capsule:
Each Capsule contains:
Pregabalin ..... 50 mg (BP Specifications)

LACPRIL 75mg Capsule:
Each Capsule contains:
Pregabalin ..... 75 mg (BP Specifications)

LACPRIL 100mg Capsule:
Each Capsule contains:
Pregabalin ..... 100 mg (BP Specifications)

LACPRIL 150mg Capsule:
Each Capsule contains:
Pregabalin ..... 150 mg (BP Specifications)

LACPRIL 300mg Capsule:
Each Capsule contains:
Pregabalin ..... 300 mg (BP Specifications)

1 INDICATIONS AND USAGE

LACPRIL is indicated for:

- Management of neuropathic pain associated with diabetic peripheral neuropathy
- Management of postherpetic neuralgia
- Adjunctive therapy for the treatment of partial onset seizures in patients 4 years of age and older
- Management of fibromyalgia
- Management of neuropathic pain associated with spinal cord injury

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

LACPRIL is given orally with or without food.

When discontinuing LACPRIL, taper gradually over a minimum of 1 week *[see Warnings and Precautions]*.

Because LACPRIL is eliminated primarily by renal excretion, adjust the dose in adult patients with reduced renal function *[see Dosage and Administration]*.

2.2 Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

The maximum recommended dose of LACPRIL 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 LACPRIL 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 recommendedd *[see Adverse Reactions]*.

2.3 Postherpetic Neuralgia

The recommended dose of LACPRIL 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 with300 mg/day, and who are able to tolerate LACPRIL, 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 Adverse Reactions]*.

2.4 Adjunctive Therapy for Partial Onset Seizures in Patients 4 Years of Age and Older

The recommended dosage for adults and pediatric patients 4 years of age and older is included in Table 1. Administer the total daily dosage orally in two or three divided doses. In pediatric patients 4 years of age and

older, the recommended dosing regimen is dependent upon body weight. Based on clinical response and tolerability, dosage may be increased, approximately weekly.

Table 1: Recommended Dosage for Adults and Pediatric Patients 4 Years and Older

Age and Body Weight	**Recommended Initial Dosage (administer in two or three divided doses)**	**Recommended Maximum Dosage (administer in two or three divided doses)**
Adults (17 years and older)	150 mg/day	600 mg/day
Pediatric patients weighing 30 kg or more	2.5 mg/kg/day	10 mg/kg/day (not to exceed 600 mg/day)
Pediatric patients weighing 11 kg to less than 30 kg	3.5 mg/kg/day	14 mg/kg/day

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

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

2.5 Management of Fibromyalgia

The recommended dose of LACPRIL 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 LACPRIL 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 Adverse Reactions]*.

2.6 Neuropathic Pain Associated with Spinal Cord Injury

The recommended dose range of LACPRIL 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) within1 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 LACPRIL may be treated with up to 300 mg two times a day *[see Clinical Studies]*.

2.7 Dosing for Adult Patients with Renal Impairment

In view of dose-dependent adverse reactions and since LACPRIL is eliminated primarily by renal excretion, adjust the dose in adult patients with reduced renal function. The use of LACPRIL 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:

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

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 LACPRIL 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**				**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 r Patients on the 75 mg QD regimen: take one supplemental dose of 100 mg or 150 mg					

TID= Three divided doses; BID = Two divided doses; QD = Single daily dose.
* Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose.
† Supplementary dose is a single additional dose.

3 DOSAGE FORMS AND STRENGTHS

Capsules: 50 mg, 75 mg, 100 mg, 150mg, 300mg

see Description and How Supplied/Storage and Handling.

4 CONTRAINDICATIONS

LACPRIL is contraindicated in patients with known hypersensitivity to pregabalin or any of its components. Angioedema and hypersensitivity reactions have occurred in patients receiving pregabalin therapy *[see Warnings and Precautions.]*

5 WARNINGS AND PRECAUTIONS

5.1 Angioedema

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

Exercise caution when prescribing LACPRIL 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.

5.2 Hypersensitivity

There have been postmarketing reports of hypersensitivity in patients shortly after initiation of treatment with LACPRIL. Adverse reactions included skin redness, blisters, hives, rash, dyspnea, and wheezing. Discontinue LACPRIL immediately in patients with these symptoms.

5.3 Increased Risk of Adverse Reactions with Abrupt or Rapid Discontinuation

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

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

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

5.4 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including LACPRIL, 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% CI: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 in Drug Patients/ 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 conring prescribing LACPRIL 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.

5.5 Peripheral Edema

LACPRIL 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 LACPRIL group compared with 2% in the placebo group. In controlled clinical trials, 0.5% of LACPRIL 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 LACPRIL 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 LACPRIL only, and 19% (23/120) of patients who were on both LACPRIL and thiazolidinedione antidiabetic agents. Similarly, weight gain was reported in 0% (0/60) of patients on thiazolidinediones only; 4% (35/859) of patients on LACPRIL 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 LACPRIL 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 LACPRIL in these patients.

5.6 Dizziness and Somnolence

LACPRIL may cause dizziness and somnolence. Inform patients that LACPRIL-related dizziness and somnolence may impair their ability to perform tasks such as driving or operating machinery *[see Patient Counseling Information.*

In the LACPRIL controlled trials in adult patients, dizziness was experienced by 30% of LACPRIL-treated patients compared to 8% of placebo-treated patients; somnolence was experienced by 23% of LACPRIL-treated patients compared to 8% of placebo-treated patients. Dizziness and somnolence generally began shortly after the initiation of LACPRIL 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 LACPRIL-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 Drug Interactions]*.

In the LACPRIL controlled trial in pediatric patients for the treatment of partial onset seizures, somnolence was experienced by 21% of LACPRIL-treated patients compared to 14% of placebo- treated patients, and occurred more frequently at higher doses.

5.7 Weight Gain

LACPRIL treatment may cause weight gain. In LACPRIL 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 LACPRIL- treated patients and 2% of placebo-treated patients. Few patients treated with LACPRIL (0.3%) withdrew from controlled trials due to weight gain. LACPRIL 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 Warnings and Precaution]*.

Although weight gain was not associated with clinically important changes in blood pressure in short-term controlled studies, the long-term cardiovascular effects of LACPRIL-associated weight gain are unknown.

Among diabetic patients, LACPRIL-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 LACPRIL for at least 2 years, the average weight gain was 5.2 kg.

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

5.8 Tumorigenic Potential

In standard preclinical *in vivo* lifetime carcinogenicity studies of LACPRIL, an unexpectedly high incidence of hemangiosarcoma was identified in two different strains of mice *[see Nonclinical Toxicology]*. The clinical significance of this finding is unknown. Clinical experience during LACPRIL'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 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 LACPRIL, it is impossible to know whether the incidence seen in these cohorts is or is not affected by treatment.

5.9 Ophthalmological Effects

In controlled studies in adult patients, a higher proportion of patients treated with LACPRIL 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 LACPRIL 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 LACPRIL, and 5% of placebo- treated patients. Visual field changes were detected in 13% of LACPRIL-treated, and 12% of placebo-treated patients. Funduscopic changes were observed in 2% of LACPRIL-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 *[see Patient Counseling Information*.

5.10 Creatine Kinase Elevations

LACPRIL treatment was associated with creatine kinase elevations. Mean changes in creatine kinase from baseline to the maximum value were 60 U/L for LACPRIL-treated patients and U/L for the placebo patients. In all controlled trials in adult patients across multiple patient

populations, 1.5% of patients on LACPRIL and 0.7% of placebo patients had a value of creatine kinase at least three times the upper limit of normal. Three LACPRIL treated subjects had events reported as rhabdomyolysis in premarketing clinical trials. The relationship between these myopathy events and LACPRIL is 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 LACPRIL if myopathy is diagnosed or suspected or if markedly elevated creatine kinase levels occur.

5.11 Decreased Platelet Count

LACPRIL treatment was associated with a decrease in platelet count. LACPRIL-treated subjects experienced a mean maximal decrease in platelet count of $20 \times 10^3/\mu L$, compared to $11 \times 10^3/\mu L$ in placebo patients. In the overall database of controlled trials in adult patients, 2% of placebo patients and 3% of LACPRIL patients experienced a potentially clinically significant decrease in platelets, defined as 20% below baseline value and less than $150 \times 10^3/\mu L$. A single LACPRIL treated subject developed severe thrombocytopenia with a platelet count less than $20 \times 10^3/\mu L$.
In randomized controlled trials, LACPRIL was not associated with an increase in bleeding-related adverse reactions.

5.12 PR Interval Prolongation

LACPRIL 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 LACPRIL 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.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Angioedema *[see Warnings and Precautions]*
- Hypersensitivity *[see Warnings and Precautions]*
- Increased Risk of Adverse Reactions with Abrupt or Rapid Discontinuation *[see*
- *Warnings and Precautions]*
- Suicidal Behavior and Ideation *[see Warnings and Precautions]*
- Peripheral Edema *[see Warnings and Precautions]*
- Dizziness and Somnolence *[see Warnings and Precautions]*
- Weight Gain *[see Warnings and Precautions]*
- Tumorigenic Potential *[see Warnings and Precautions]*
- Ophthalmological Effects *[see Warnings and Precautions]*
- Creatine Kinase Elevations *[see Warnings and Precautions]*
- Decreased Platelet Count *[see Warnings and Precautions]*
- PR Interval Prolongation *[see Warnings and Precautions]*

Other Adverse Reactions Observed During the Clinical Studies of LACPRIL

Following is a list of treatment-emergent adverse reactions reported by patients treated with LACPRIL 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 reactions are those occurring on one or more occasions in at least 1/100 patients; *infrequent* adverse reactions are those occurring in 1/100 to
1/1000 patients; *rare* reactions are those occurring in fewer than 1/1000 patients. Events of major clinical importance are described in the *Warnings and Precautions* section.

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

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, Periodontal abscess

Hemic and Lymphatic System – *Frequent:* Ecchymosis; *Infrequent:* 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

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

Nervous System – *Frequent:* Anxiety, Depersonalization, Hypertonia, Hypoesthesia, Libido decreased, Nystagmus, Paresthesia, Sedation, 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-Barré syndrome, Hypalgesia, Intracranial hypertension, Manic reaction, Paranoid reaction, Peripheral neuritis, Personality disorder, Psychotic depression, Schizophrenic reaction, Sleep disorder, 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, Nail Disorder, 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, Cornealulcer, 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, Urine abnormality; *Rare:* Acute kidney failure, Balanitis, Bladder Neoplasm, Cervicitis, Dyspareunia, Epididymitis, Female lactation, Glomerulitis, Ovarian disorder, Pyelonephritis

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.

6.1 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of LACPRIL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Nervous System Disorders – Headache

Gastrointestinal Disorders – Nausea, Diarrhea

Reproductive System and Breast Disorders – Gynecomastia, Breast Enlargement

In addition, there are postmarketing reports of events related to reduced lower gastrointestinal tract function (e.g., intestinal obstruction, paralytic ileus, constipation) when LACPRIL was co-administered with medications that have the potential to produce constipation, such as opioid analgesics. There are also postmarketing reports of respiratory failure and coma in patients taking pregabalin and other CNS depressant medications.

7 DRUG INTERACTIONS

Since LACPRIL is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (less than 2% of a dose recovered in urine as metabolites), and does not bind to plasma proteins, its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions or protein binding displacement. *In vitro* and *in vivo* studies showed that LACPRIL 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 LACPRIL and commonly used antiepileptic drugs *[see Clinical Pharmacology]*.

Pharmacodynamics

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to LACPRIL during pregnancy. To provide information regarding the effects of *in utero* exposure to LACPRIL, physicians are advised to recommend that pregnant patients taking LACPRIL enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves.

Risk Summary

There are no adequate and well-controlled studies with LACPRIL in pregnant women.

However, in animal reproduction studies, increased incidences of fetal structural abnormalities and other manifestations of developmental toxicity, including skeletal malformations, retarded ossification, and decreased fetal body weight were observed in the offspring of rats and rabbits given pregabalin orally during organogenesis, at doses that produced plasma pregabalin exposures (AUC) greater than or equal to 16 times human exposure at the maximum recommended dose (MRD) of 600 mg/day *[see Data]*. In an animal development study, lethality, growth retardation, and nervous and reproductive system functional impairment were observed in the offspring of rats given pregabalin during gestation and lactation. The no-effect dose for developmental toxicity was approximately twice the human exposure at MRD. The background risk of major birth defects and miscarriage for the indicated populations are unknown. However, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies. Advise pregnant women of the potential risk to a fetus.

8.2 Lactation

Risk Summary

Small amounts of pregabalin have been detected in the milk of lactating women. A pharmacokinetic study in lactating women detected pregabalin in breast milk at average steady state concentrations approximately 76% of those in maternal plasma. The estimated average daily infant dose of pregabalin from breast milk (assuming mean milk consumption of 150 mL/kg/day) was 0.31 mg/kg/day, which on a mg/kg basis would be approximately 7% of the maternal dose *[see Data]*. The study did not evaluate the effects of LACPRIL on milk production or the effects of LACPRIL on the breastfed infant.

Based on animal studies, there is a potential risk of tumorigenicity with pregabalin exposure via breast milk to the breastfed infant *[see Nonclinical Toxicology*. Available clinical study data in patients greater than 12 years of age do not provide a clear conclusion about the potential risk of tumorigenicity with pregabalin *[see Warnings and Precautions*. Because of the potential risk of tumorigenicity, breastfeeding is not recommended during treatment with LACPRIL.

Data

A pharmacokinetic study in ten lactating women, who were at least 12 weeks postpartum, evaluated the concentrations of pregabalin in plasma and breast milk. LACPRIL 150 mg oralcapsule was given every 12 hours (300 mg daily dose) for a total of four doses. Pregabalin was detected in breast milk at average steady-state concentrations approximately 76% of those in maternal plasma. The estimated average daily infant dose of pregabalin from breast milk (assuming mean milk consumption of 150 mL/kg/day) was 0.31 mg/kg/day, which on a mg/kg basis would be approximately 7% of the maternal dose. The study did not evaluate the effects of LACPRIL on milk production. Infants did not receive breast milk obtained during the dosing period, therefore, the effects of LACPRIL on the breast fed infant were not evaluated.

8.3 Females and Males of Reproductive Potential

Infertility

Male

Effects on Spermatogenesis

In a randomized, double-blind, placebo-controlled non-inferiority study to assess the effect of pregabalin on sperm characteristics, healthy male subjects received pregabalin at a daily dose up to 600 mg (n=111) or placebo (n=109) for 13 weeks (one complete sperm cycle) followed by a 13-week washout period (off-drug). A total of 65 subjects in the pregabalin group (59%) and 62 subjects in the placebo group (57%) were included in the per protocol (PP) population. These subjects took study drug for at least 8 weeks, had appropriate timing of semen collections and did not have any significant protocol violations. Among these subjects, approximately 9% of the pregabalin group (6/65) vs. 3% in the placebo group (2/62) had greater than or equal to 50% reduction in mean sperm concentrations from baseline at Week 26 (the primary endpoint). The difference between pregabalin and placebo was within the pre-specified non-inferiority margin of 20%. There were no adverse effects of pregabalin on sperm morphology, sperm motility, serum FSH or serum testosterone levels as compared to placebo. In subjects in the PP population with greater than or equal to 50% reduction in sperm concentration from baseline, sperm concentrations were no longer reduced by greater than or equal to 50% in any affected subject after an additional 3 months off-drug. In one subject, however, subsequent semen analyses demonstrated reductions from baseline of greater than or equal to 50% at 9 and 12 months off-drug. The clinical relevance of these data is unknown.

In the animal fertility study with pregabalin in male rats, adverse reproductive and developmental effects were observed *[see Nonclinical Toxicology]*.

8.4 Pediatric Use

Neuropathic Pain Associated with Diabetic Peripheral Neuropathy, Postherpetic Neuralgia, and Neuropathic Pain Associated with Spinal Cord Injury

Safety and effectiveness in pediatric patients have not been established. Fibromyalgia

Safety and effectiveness in pediatric patients have not been established.

A 15-week, placebo-controlled trial was conducted with 107 pediatric patients with fibromyalgia, ages 12 through 17 years, at LACPRIL total daily doses of 75-450 mg per day. The primary efficacy endpoint of change from baseline to Week 15 in mean pain intensity (derived from an 11-point numeric rating scale) showed numerically greater improvement for the pregabalin-treated patients compared to placebo-treated patients, but did not reach statistical significance. The most frequently observed adverse reactions in the clinical trial included dizziness, nausea, headache, weight increased, and fatigue. The overall safety profile in adolescents was similar to that observed in adults with fibromyalgia.

Adjunctive Therapy for Partial Onset Seizures

The safety and effectiveness of LACPRIL as adjunctive treatment for partial onset seizures in pediatric patients 4 to less than 17 years of age have been established in a 12-week, double-blind, placebo-controlled study (n = 295) *[see Clinical Studies*. Patients treated with LACPRIL
10 mg/kg/day had, on average, a 21.0% greater reduction in partial onset seizures than patients treated with placebo (p = 0.0185). Patients treated with LACPRIL 2.5 mg/kg/day had, on average, a 10.5% greater reduction in partial onset seizures than patients treated with placebo, but the
difference was not statistically significant (p = 0.2577).

Responder rates (50% or greater reduction in partial onset seizure frequency) were a key secondary efficacy parameter and showed numerical improvement with LACPRIL compared with placebo: the responder rates were 40.6%, 29.1%, and 22.6%, for LACPRIL 10 mg/kg/day, LACPRIL 2.5 mg/kg/day, and placebo, respectively.

The most common adverse reactions (≥5%) with LACPRIL in this study were somnolence, weight increased, and increased appetite *[see Adverse Reactions]*.

The use of LACPRIL 2.5mg/kg/day in pediatric patients is further supported by evidence from adequate and well controlled studies in adults with partial-onset seizures and pharmacokinetic data from adult and pediatric patients *[see Clinical Pharmacology]*.

Safety and effectiveness in patients less than 4 years of age have not been established.

Juvenile Animal Data

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 greater than or equal to 50 mg/kg. The neurobehavioral changes of acoustic startle persisted at greater than or equal to 250 mg/kg and locomotor activity and water maze performance at greater than or equal to 500 mg/kg in animals tested after cessation of dosing and, thus, were considered to represent long-term effects. The low effect dose for developmental neurotoxicity and reproductive impairment in juvenile rats (50 mg/kg) was associated with a plasma pregabalin exposure (AUC) approximately equal to human exposure at the maximum recommended dose of 600 mg/day. A no-effect dose was not established.

LACPRIL is known to be substantially excreted by the kidney, and the risk of toxic reactions to LACPRIL may be greater in patients with impaired renal function. Because LACPRIL is eliminated primarily by renal excretion, adjust the dose for elderly patients with renal impairment *[see Dosage and Administration]*.

8.5 Renal Impairment

LACPRIL is eliminated primarily by renal excretion and dose adjustment is recommended for adult patients with renal impairment *[see Dosage and Administration and Clinical Pharmacology*. The use of LACPRIL in pediatric patients with compromised renal function has not been studied.

9 OVERDOSAGE

Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans

There is limited experience with overdose of LACPRIL. The highest reported accidental overdose of LACPRIL during the clinical development program was 8000 mg, and there were no notable clinical consequences.
Treatment or Management of Overdose

There is no specific antidote for overdose with LACPRIL. 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 LACPRIL.

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).

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

LACPRIL (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.

10.2 Pharmacokinetics

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

<u>Absorption and Distribution</u>

Following oral administration of LACPRIL 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.

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 mn elimination half-life of 6.3 hours in subjects with normal renal function. Meanrenal 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 Dosage and Administration]*.

11 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide). Angioedema

Advise patients that LACPRIL may cause angioedema, with swelling of the face, mouth (lip, gum, tongue) and neck (larynx and pharynx) that can lead to life-threatening respiratory compromise. Instruct patients to discontinue LACPRIL and immediately seek medical care if they experience these symptoms [*see Warnings and Precautions]*.

Hypersensitivity

Advise patients that LACPRIL has been associated with hypersensitivity reactions such as wheezing, dyspnea, rash, hives, and blisters. Instruct patients to discontinue LACPRIL and immediately seek medical care if they experience these symptoms *[see Warnings and Precautions]*.

Adverse Reactions with Abrupt or Rapid Discontinuation

Advise patients to take LACPRIL as prescribed. Abrupt or rapid discontinuation may result in increased seizure frequency in patients with seizure disorders, and insomnia, nausea, headache, anxiety, hyperhidrosis, or diarrhea *[see Warnings and Precautions]*.

Suicidal Thinking and Behavior

Patients, their caregivers, and families should be counseled that AEDs, including LACPRIL, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood orbehavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Report behaviors of concern immediately to healthcare providers *[see Warnings and Precautions]*.

Dizziness and Somnolence

Counsel patients that LACPRIL may cause dizziness, somnolence, blurred vision and other CNS signs and symptoms. Accordingly, advise patients not to drive, operate complex machinery, or engage in other hazardous activities until they have gained sufficient experience on LACPRIL to gauge whether or not it affects their mental, visual, and/or motor performance adversely *[see Warnings and Precautions]*.

Weight Gain and Edema

Counsel patients that LACPRIL may cause edema and weight gain. Advise patients that concomitant treatment with LACPRIL 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 *[see Warnings and Precautions]*.

Ophthalmological Effects

Counsel patients that LACPRIL may cause visual disturbances. Inform patients that if changes in vision occur, they should notify their physician *[see Warnings and Precautions]*.

Creatine Kinase Elevations

Instruct patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever *[see Warnings and Precautions]*.

CNS Depressants

Inform patients who require concomitant treatment with central nervous system depressants such as opiates or benzodiazepines that they may experience additive CNS side effects, such as somnolence *[see Warnings and Precautions (5.6) and Drug Interactions]*.

Alcohol

Tell patients to avoid consuming alcohol while taking LACPRIL, as LACPRIL may potentiate the impairment of motor skills and sedating effects of alcohol.

Missed Dose
Counsel patients if they miss a dose, they should take it as soon as they remember. If it is almost time for the next dose, they should skip the missed dose and take the next dose at their regularly scheduled time. Instruct patients not to take two doses at the same time.Pregnancy

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to LACPRIL during pregnancy *[see Use in Specific Populations]*.

Lactation

Advise nursing mothers that breastfeeding is not recommended during treatment with LACPRIL *[*see *Use in Specific Populations]*.

Male Fertility

Inform men being treated with LACPRIL who plan to father a child 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 Nonclinical Toxicology and Use in Specific populations]*.

Dermatopathy

Instruct diabetic patients to pay particular attention to skin integrity while being treated with LACPRIL and to inform their healthcare provider about any sores or skin problems. Some animals treated with pregabalin developed skin ulcerations, although no increased incidence of skin lesions associated with LACPRIL was observed in clinical trials *[see Nonclinical Toxicology]*.

HOW SUPPLIED:

LACPRIL capsule 50mg is available in
Alu. Alu. Blister pack containing 14's capsules

LACPRIL capsule 75mg is available in
Alu. Alu. Blister pack containing 14's capsules

LACPRIL capsule 100mg is available in
Alu. Alu. Blister pack containing 14's capsules

LACPRIL capsule 150mg is available in
Alu. Alu. Blister pack containing 14's capsules

LACPRIL capsule 300mg is available in
Alu. Alu. Blister pack containing 14's capsules

PRECAUTION & STORAGE CONDITIONS:

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

لیک پرل کیپسولز

(پری گیبلین)

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

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