Balinozar 75 mg Hard gelatin capsule

Balinozar 150 mg Hard gelatin capsule

INDICATIONS AND USAGE

Balinozar is indicated for:

- **Management of neuropathic pain associated with diabetic peripheral neuropathy**
- **Management of postherpetic neuralgia**
- **Adjunctive therapy for adult patients with partial onset seizures**
- **Management of fibromyalgia**
- **Management of neuropathic pain associated with spinal cord injury**

DOSAGE AND ADMINISTRATION

Balinozar is given orally with or without food.

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

Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

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

Although Balinozar was also studied at 600 mg/day, there is no evidence that this dose confers additional significant benefit and this dose was less well tolerated. In view of the dose-dependent adverse reactions, treatment with doses above 300 mg/day is not recommended *[see Adverse Reactions]*.

Postherpetic Neuralgia

The recommended dose of Balinozar is 75 to 150 mg two 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 (150 mg/day). The dose may be increased to 300 mg/day within 1 week based on efficacy and tolerability. Because Balinozar is eliminated primarily by renal excretion, adjust the dose in patients with reduced renal function *[see Dosage and Administration (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, may be treated with up to 300 mg two times a day (600 mg/day). In view of the dose-dependent adverse reactions and the higher rate of treatment discontinuation due to Balinozar 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]*.

Adjunctive Therapy for Adult Patients with Partial Onset Seizures

Pregabalin at doses of 150 to 600 mg/day has been shown to be effective as adjunctive therapy in the treatment of partial onset seizures in adults. Both the efficacy and adverse event profiles of Pregabalin have been shown to be dose-related. Administer the total daily dose in two or three divided doses. In general, it is recommended that patients be started on a total daily dose no greater than 150 mg/day (75 mg two times a day). Based on individual patient response and tolerability, the dose may be increased to a maximum dose of 600 mg/day.

Because Pregabalin is eliminated primarily by renal excretion, adjust the dose in patients with reduced renal function *[see Dosage and Administration (Patients with Renal Impairment)]*.

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

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

Management of Fibromyalgia

The recommended dose of Balinozar for fibromyalgia is 300 to 450 mg/day. Begin dosing at 75 mg two times a day (150 mg/day). The dose may be increased to 150 mg two times a day (300 mg/day) within 1 week based on efficacy and tolerability. Patients who do not experience sufficient benefit with 300 mg/day may be further increased to 225 mg two times a day (450 mg/day). Although Pregabalin was also studied at 600 mg/day, there is no evidence that this dose confers additional benefit and this dose was less well tolerated. In view of the dose- dependent adverse reactions, treatment with doses above 450 mg/day is not recommended *[see Adverse Reactions]*. Because Pregabalin is eliminated primarily by renal excretion, adjust the dose in patients with reduced renal function *[see Dosage and Administration (Patients with Renal Impairment)]*.

Neuropathic Pain Associated with Spinal Cord Injury

The recommended dose range of Balinozar for the treatment of neuropathic pain associated with spinal cord injury is 150 to 600 mg/day. The recommended starting dose is 75 mg two times a day (150 mg/day). The dose may be increased to 150 mg two times a day (300 mg/day) within 1 week based on efficacy and tolerability. Patients who do not experience sufficient pain relief after 2 to 3 weeks of treatment with 150 mg two times a day and who tolerate Pregabalin may be treated with up to 300 mg two times a day. Because Pregabalin is eliminated primarily by renal excretion, adjust the dose in patients with reduced renal function *[see Dosage and Administration (Patients with Renal Impairment)]*.

Patients with Renal Impairment

In view of dose-dependent adverse reactions and since Pregabalin is eliminated primarily by renal excretion, adjust the dose in patients with reduced renal function. Base the dose adjustment in patients with renal impairment on creatinine clearance (CLcr), as indicated in Table 1. To use this dosing table, an estimate of the patient's CLcr in mL/min is needed. CLcr in mL/min may be estimated from serum creatinine (mg/dL) determination using the Cockcroft and Gault equation:

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

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 1 to determine the corresponding renal adjusted dose.

(For example: A patient initiating Balinozar 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 1).

Table 1. Pregabalin Dosage Adjustment Based on Renal Function

Creatinine Clearance (CLcr) (mL/min)	Total Pregabalin Daily Dose (mg/day)*				Dose Regimen
≥60	150	300	450	600	BID or TID
30–60	75	150	225	300	BID or TID
15–30	25–50	75	100–150	150	QD or BID
<15	25	25–50	50–75	75	QD
Supplementary dosage following hemodialysis (mg)†					
Patients on the 25 mg QD regimen: take one supplemental dose of 25 mg or 50 mg Patients on the 25–50 mg QD regimen: take one supplemental dose of 50 mg or 75 mg Patients on the 50–75 mg QD regimen: take one supplemental dose of 75 mg or 100 mg Patients on the 75 mg QD regimen: take one supplemental dose of 100 mg or 150 mg					

TID= Three divided doses; BID = Two divided doses; QD = Single daily dose.

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

† Supplementary dose is a single additional dose.

DOSAGE FORMS AND STRENGTHS

Capsules: 75 mg and 150 mg
[see Description and How Supplied/Storage and Handling].

CONTRAINDICATIONS

Balinozar 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.

WARNINGS AND PRECAUTIONS

Respiratory depression

There have been reports of severe respiratory depression in relation to pregabalin use. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment, concomitant use of CNS depressants and the elderly may be at higher risk of experiencing this severe adverse reaction. Dose adjustments may be necessary in these patients

Angioedema

There have been postmarketing reports of angioedema in patients during initial and chronic treatment with pregabalin. Specific symptoms included swelling of the face, mouth (tongue, lips, and gums), and neck (throat and larynx). There were reports of life-threatening angioedema with respiratory compromise requiring emergency treatment. Discontinue Balinozar immediately in patients with these symptoms.

Exercise caution when prescribing Balinozar to patients who have had a previous episode of angioedema. In addition, patients who are taking other drugs associated with angioedema (e.g., angiotensin converting enzyme inhibitors [ACE-inhibitors]) may be at increased risk of developing angioedema.

Hypersensitivity

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

Withdrawal of Antiepileptic Drugs (AEDs)

As with all AEDs, withdraw Balinozar gradually to minimize the potential of increased seizure frequency in patients with seizure disorders. If Balinozar is discontinued, taper the drug gradually over a minimum of 1 week.

Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including Balinozar, 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.

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.

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

Anyone considering prescribing Balinozar 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.

Inform patients, their caregivers, and families that Balinozar and other AEDs increase the risk of suicidal thoughts and behavior and advise them of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Report behaviors of concern immediately to healthcare providers.

Peripheral Edema

Balinozar 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.

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 Balinozar and these agents.

Because there are limited data on congestive heart failure patients with New York Heart Association (NYHA) Class III or IV cardiac status, exercise caution when using pregabalin in these patients.

Dizziness and Somnolence

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

Weight Gain

Balinozar treatment may cause weight gain.
Balinozar 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 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). 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}).

Abrupt or Rapid Discontinuation

Following abrupt or rapid discontinuation of Balinozar, some patients reported symptoms including insomnia, nausea, headache, anxiety, hyperhidrosis, and diarrhea. Taper Balinozar gradually over a minimum of 1 week rather than discontinuing the drug abruptly.

Tumorigenic Potential

In standard preclinical *in vivo* lifetime carcinogenicity studies of pregabalin, an unexpectedly high incidence of hemangiosarcoma was identified in two different strains of mice. The clinical significance of this finding is unknown. Clinical experience during LYRICA's premarketing development provides no direct means to assess its potential for inducing tumors in humans.

Ophthalmological Effects

In controlled studies, a higher proportion of patients treated with pregabalin reported blurred vision (7%) , 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, visual acuity was reduced in 7% of patients treated with pregabalin. Visual field changes were detected in 13% of pregabalin -treated. Funduscopic changes were observed in 2% of pregabalin -treated.

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

Creatine Kinase Elevations

Balinozar 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 patient . In all controlled trials across multiple patient populations, 1.5% of patients on pregabalin 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. 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 Balinozar if myopathy is diagnosed or suspected or if markedly elevated creatine kinase levels occur.

Decreased Platelet Count

Balinozar treatment was associated with a decrease in platelet count. pregabalin -treated subjects experienced a mean maximal decrease in platelet count of $20 \times 10^3/\mu L$. In the overall database of controlled trials 3% of pregabalin 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 pregabalin treated subject developed severe thrombocytopenia with a platelet count less than $20 \times 10^3/ \mu L$. In randomized controlled trials, pregabalin was not associated with an increase in bleeding-related adverse reactions.

PR Interval Prolongation

Pregabalin treatment was associated with PR interval prolongation. In analyses of clinical trial ECG data, the mean PR interval increase was 3–6 msec at Pregabalin doses 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.

- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucosegalactose malabsorption should not take this medicine

ADVERSE REACTIONS

Respiratory, thoracic and mediastinal disorders
Frquency "not known": Respiratory depression

Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

Most Common Adverse Reactions

Table 2 lists all adverse reactions, regardless of causality, occurring in greater than or equal to 1% of patients with neuropathic pain associated with diabetic neuropathy

Adverse Reactions Leading to Discontinuation

In the Balinozar treatment group, the most common reasons for discontinuation due to adverse reactions were dizziness and somnolence. In comparison, less than 1% of placebo patients withdrew due to dizziness and somnolence. Other reasons for discontinuation from the trials, occurring with greater frequency in the LYRICA group than in the placebo group, were asthenia, confusion, and peripheral edema. Each of these events led to withdrawal in approximately 1% of patients.

Treatment-emergent adverse reaction incidence in neuropathic pain associated with diabetic peripheral neuropathy

Body system Preferred term

Body as a whole

Asthenia
Accidental injury
Back pain
Chest pain
Face edema
Digestive system
Dry mouth
Constipation
Flatulence
Metabolic and nutritional disorders
Peripheral edema
Weight gain
Edema
Hypoglycemia
Nervous system
Dizziness
Somnolence
Neuropathy
Ataxia
Vertigo
Confusion
Euphoria
Incoordination

Thinking abnormal†

Tremor
Abnormal gait

Amnesia

Nervousness

Respiratory system
Dyspnea
Special senses
Blurry vision‡

Abnormal vision

* PGB: pregabalin

† 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.

‡ Investigator term; summary level term is amblyopia

Postherpetic Neuralgia

Adverse Reactions Leading to Discontinuation

In the treatment group, the most common reasons for discontinuation due to adverse reactions 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 Reactions

Table 3 lists all adverse reactions, regardless of causality, occurring in greater than or equal to 1% of patients with neuropathic pain associated with postherpetic neuralgia

Table 3. Treatment-emergent adverse reaction incidence in neuropathic pain associated with postherpetic neuralgia

Body system Preferred term

Body as a whole
Infection
Headache
Pain
Accidental injury
Flu syndrome
Face edema
Digestive system
Dry mouth
Constipation
Flatulence
Vomiting

Metabolic and nutritional disorders
Peripheral edema
Weight gain
Edema
Musculoskeletal system
Myasthenia
Nervous system
Dizziness
Somnolence
Ataxia
Abnormal gait
Confusion
Thinking abnormal†
Incoordination
Amnesia
Speech disorder
Respiratory system
Bronchitis
Special senses
Blurry vision‡
Diplopia
Abnormal vision
Eye Disorder
Urogenital System
Urinary Incontinence

* PGB: pregabalin

† 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.

‡ Investigator term; summary level term is amblyopia

Adjunctive Therapy for Adult Patients with Partial Onset Seizures

Adverse Reactions Leading to Discontinuation

In the pregabalin treatment group, the adverse reactions most frequently leading to discontinuation were dizziness (6%), ataxia (4%), and somnolence (3%). In comparison, less than 1% of patients in the placebo group withdrew due to each of these events. Other adverse reactions 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 Reactions

lists all dose-related adverse reactions occurring in at least 2% of all pregabalin -treated patients.

Dose-related treatment-emergent adverse reaction incidence in adjunctive therapy for adult patients with partial onset seizures

Body System Preferred Term	
Body as a Whole	
Accidental Injury	
Pain	
Digestive System	
Increased Appetite	
Dry Mouth	
Constipation	
Metabolic and Nutritional Disorders	
Weight Gain	
Peripheral Edema	
Nervous System	
Dizziness	
Somnolence	
Ataxia	
Tremor	
Thinking Abnormal‡	
Amnesia	
Speech Disorder	
Incoordination	
Abnormal Gait	
Twitching	
Confusion	
Myoclonus	
Special Senses	
Blurred Vision§	
Diplopia	
Abnormal Vision	

* PGB: pregabalin

† Excludes patients who received the 50 mg dose in Study E1.

‡ 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.

§ Investigator term; summary level term is amblyopia.

Fibromyalgia

Adverse Reactions Leading to Discontinuation

In the pregabalin treatment group, the most common reasons for discontinuation due to adverse reactions were dizziness (6%) and somnolence (3%). In comparison, less than 1% of placebo-treated patients withdrew due to dizziness and somnolence. Other reasons for discontinuation from the trials, occurring with greater frequency in the pregabalin treatment group than in the placebo treatment group, were fatigue, headache, balance disorder, and weight increased. Each of these adverse reactions led to withdrawal in approximately 1% of patients.

Most Common Adverse Reactions

Table 5 lists all adverse reactions, regardless of causality, occurring in greater than or equal to 2% of patients with fibromyalgia

Treatment-emergent adverse reaction incidence in fibromyalgia

System Organ Class Preferred term

Ear and Labyrinth Disorders

Vertigo
Eye Disorders
Vision blurred
Gastrointestinal Disorders
Dry mouth
Constipation
Vomiting
Flatulence
Abdominal distension
General Disorders and Administrative Site Conditions
Fatigue
Edema peripheral
Chest pain
Feeling abnormal
Edema
Feeling drunk
Infections and Infestations

Sinusitis
Investigations
Weight increased
Metabolism and Nutrition Disorders
Increased appetite
Fluid retention
Musculoskeletal and Connective Tissue
Arthralgia
Muscle spasms
Back pain
Nervous System Disorders
Dizziness

Somnolence
Headache
Disturbance in attention
Balance disorder
Memory impairment
Coordination abnormal
Hypoesthesia
Lethargy
Tremor
Psychiatric Disorders
Euphoric Mood
Confusional state
Anxiety
Disorientation
Depression
Respiratory, Thoracic and Mediastinal Disorders
Pharyngolaryngeal pain

* PGB: pregabalin

Neuropathic Pain Associated with Spinal Cord Injury

Adverse Reactions Leading to Discontinuation

In the pregabalin treatment group, the most common reasons for discontinuation due to adverse reactions were somnolence (3%) and edema (2%). In comparison, none of the placebo-treated patients withdrew due to somnolence and edema. Other reasons for discontinuation from the trials, occurring with greater frequency in the pregabalin treatment group than in the placebo treatment group, were fatigue and balance disorder. Each of these adverse reactions led to withdrawal in less than 2% of patients.

Most Common Adverse Reactions

Table 6 lists all adverse reactions, regardless of causality, occurring ingreater than or equal to 2% of patients with neuropathic pain associated with spinal cord injury

Treatment-emergent adverse reaction incidence in neuropathic pain associated with spinal cord injury

System Organ Class
Preferred term
Ear and labryrinth
Vertigo
Eye disorders
Vision blurred
Gastrointestinal disorders
Dry mouth
Constipation
Nausea
Vomiting
General disorders and administration site conditions
Fatigue

Edema peripheral
Edema
Pain
Infections and infestations
Nasopharyngitis
Investigations
Weight increased
Blood creatine phosphokinase increased
Musculoskeletal and connective tissue
Muscular weakness
Pain in extremity
Neck pain
Back pain
Joint swelling
Nervous system disorders
Somnolence
Dizziness
Disturbance in attention
Memory impairment
Paresthesia
Psychiatric disorders
Insomnia
Euphoric mood
Renal and urinary
Urinary incontinence
Skin and subcutaneous tissue disorders
Decubitus ulcer
Vascular disorders
Hypertension
Hypotension

* PGB: pregabalin

Other Adverse Reactions of pregabalin

Following is a list of treatment-emergent adverse reactions reported by patients treated with pregabalin 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
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, 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, 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.

Other Adverse reaction

Nervous System Disorders – Headache Gastrointestinal Disorders

– Nausea, Diarrhea

Reproductive System and Breast Disorders – Gynecomastia, Breast Enlargement

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

DRUG INTERACTIONS

Since pregabalin 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 pregabalin is unlikely to be involved in significant pharmacokinetic drug interactions.
Specifically, there are no pharmacokinetic interactions between pregabalin and the following antiepileptic drugs: carbamazepine, valproic acid, lamotrigine, phenytoin, phenobarbital, and topiramate. Important pharmacokinetic interactions would also not be expected to occur between pregabalin and commonly used antiepileptic drugs *[see Clinical Pharmacology]*.

Pharmacodynamics

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary
There are no adequate and well-controlled studies with pregabalin in pregnant women.
The background risk of major birth defects and miscarriage for the indicated populations are unknown

Lactation

Risk Summary
Small amounts of pregabalin have been detected in the milk of lactating women.

Females and Males of Reproductive Potential

Infertility

Male

Effects on Spermatogenesis

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

Pediatric Use

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

Geriatric Use

No overall differences in safety and efficacy were observed between these patients and younger patients. 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, adjust the dose for elderly patients with renal impairment *[see Dosage and Administration]*.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

Balinozar is a Schedule V controlled substance.

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

Abuse

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).

Dependence

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

OVERDOSAGE

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.

Treatment or Management of Overdose

There is no specific antidote for overdose with Pregabalin. If indicated, elimination of unabsorbed drug may be attempted by emesis or gastric lavage; observe usual precautions to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient. 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).

DESCRIPTION

Balinozar (pregabalin) Capsules are administered orally and are supplied as imprinted hard-shell capsules containing 75, 150 mg of pregabalin, along with lactose monohydrate, magnesium stearate, and talc as inactive ingredients. The capsule shells of balinozar 75 mg contain gelatin and titanium dioxide. In addition, quinolone yellow, carmosine red, ponceau red and brilliant blue. The capsule shells of balinozar 150 mg contain gelatin and titanium dioxide. In addition, quinolone yellow, ponceau red and brilliant blue

CLINICAL PHARMACOLOGY

Mechanism of Action

Pregabalin binds with high affinity to the alpha2-delta site (an auxiliary subunit of voltage-gated calcium channels) in central nervous system tissues. Although the mechanism of action of pregabalin has not been fully elucidated, results with genetically modified mice and with compounds structurally related to pregabalin (such as gabapentin) suggest that binding to the alpha2-delta subunit may be involved in pregabalin's anti-nociceptive and antiseizure effects in animals. In animal models of nerve damage, pregabalin has been shown to reduce calcium- dependent release of pro-nociceptive neurotransmitters in the spinal cord, possibly by disrupting alpha2-delta containing-calcium channel trafficking and/or reducing calcium currents. Evidence from other animal models of nerve damage and persistent pain suggest the anti-nociceptive activities of pregabalin may also be mediated through interactions with descending noradrenergic and serotonergic pathways originating from the brainstem that modulate pain transmission in the spinal cord.

While pregabalin is a structural derivative of the inhibitory neurotransmitter 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 LYRICA 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 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 Dosage and Administration]*.

Pharmacokinetics in Special Populations

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 (2.6)*].

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, (2.6)*].

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. In vitro drug interaction studies demonstrate that pregabalin does not induce CYP1A2 or CYP3A4 activity. Therefore, an increase in the metabolism of coadministered CYP1A2 substrates (e.g. theophylline, caffeine) or CYP 3A4 substrates (e.g., midazolam, testosterone) is not anticipated.

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

HOW SUPPLIED/STORAGE AND HANDLING

Storage:

Balinozar 75 mg Hard gelatin capsule

Store at temperature not exceeding 30°C, in dry place

Balinozar 150 mg Hard gelatin capsule

Store at temperature not exceeding 30°C, in dry place

Pack:

Balinozar 75 mg Hard gelatin capsule

Carton box containing 2 (Al/opaque PVC) strips each of 10 hard gelatin capsules and an inner leaflet

Balinozar 150 mg Hard gelatin capsule

Carton box containing 2 (Al/opaque PVC) strips each of 10 hard gelatin capsules and an inner leaflet

Manufactured by Pharma Cure Pharmaceutical Industries