approximately 12 hours and AUC is 99% relative to a comparative dose of Revogab CR. AUC decreases approximately 13% to 25% when pregabalin extended-release tablets is administered following a 400 to 500 calorie or 600 to 750 calorie (50% carbohydrates, 20% protein, 30% fat) morning meal relative to the 800 to 1000 calorie meal, while C max remains the same.

Distribution
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.

Elimination
Metabolism: 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.

Excretion: 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 CLcr

Incompatibilities: Not applicable
Shelf life: 2 years

Nature and contents of container and special equipment for use/administration or Implantation:
The container closure system Alu-Alu blisters of pack sizes 10's and 30's in a secondary unit carton.

Special precautions for disposal: No special requirements

STORAGE CONDITIONS AND INSTRUCTIONS
• Store below 30˚C in a dry place, protect from light.
• To be dispensed on the prescription of a registered medical practitioner only.
• Keep out of the reach of children.

ہدایات:
- **خوراک** ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
- دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر روشنی سے بچا کر خشک جگہ پر رکھیں۔
- صرف رجسٹرڈ ڈاکٹرز کے نسخے پر ہی فروخت کریں۔
- بچوں کی پہنچ سے دور رکھیں۔

Manufactured by:
Kaizen Pharmaceuticals (Pvt.) Ltd.
E-127-129, North Western Industrial Zone,
Bin Qasim, Karachi-75020, Pakistan.

ART No. 980

REVOGAB CR
(P r e g a b a l i n)

ریووگیب سی آر
(پریگیبلین)

82.5 mg, 165 mg & 330 mg Tablet

۸۲.۵ ملی گرام، ۱۶۵ ملی گرام
اور ۳۳۰ ملی گرام گولیاں

Composition:
Revogab CR 82.5mg Tablet
Each Extended release film coated tablet contains:
Pregabalin..... 82.5mg

Revogab CR 165mg Tablet
Each Extended release film coated tablet contains:
Pregabalin..... 165mg

Revogab CR 330mg Tablet
Each Extended release film coated tablet contains:
Pregabalin..... 330mg

Pharmaceutical form: Tablet

QUALITATIVE AND QUANTITATIVE COMPOSITIONS:
Qualitative Declaration: Pregabalin

Quantitative declaration:
pregabalin.....82.5mg
pregabalin.....165mg
pregabalin.....330mg

Revogab CR is indicated for the management of:
• Neuropathic pain associated with diabetic peripheral neuropathy (DPN)
• Postherpetic neuralgia (PHN) (1)

INDICATIONS AND USAGE FOR Revogab CR TABLETS
Revogab CR extended-release tablets are indicated for the management of:
• Neuropathic pain associated with diabetic peripheral neuropathy (DPN)
• Postherpetic neuralgia (PHN)
Efficacy of Revogab CR extended-release tablets has not been established for the management of fibromyalgia or as adjunctive therapy for adult patients with partial onset seizures.

Revogab CR Tablets Dosage and Administration
• Revogab CR extended-release tablets should be administered once daily after an evening meal. It should be swallowed whole and should not be split, crushed, or chewed.
• Dosing recommendations for Revogab CR extended-release tablets:

Indication	Dosing Regimen	Initial Dose	Maximum Dose
DPN Pain	Single dose per day	165 mg/day	330 mg/day within 1 week.
PHN	Single dose per day	165 mg/day	330 mg/day within 1 week. Maximum dose of 660 mg/day.

Dosage Forms and Strengths
Revogab CR Extended-release tablets: 82.5 mg, 165 mg, and 330 mg.
Contraindications
Known hypersensitivity to pregabalin or any of its components.

WARNINGS AND PRECAUTIONS
• **Angioedema:** Angioedema [e.g., swelling of the face, mouth (tongue, lips, and gums) and neck (throat and larynx)] can occur and may be associated with life-threatening respiratory compromise requiring emergency treatment. Discontinue Revogab CR extended-release tablets immediately in patients with these symptoms.

• **Hypersensitivity reactions:** Hypersensitivity reactions (e.g., hives, dyspnea, and wheezing) can occur. Discontinue Revogab CR extended-release tablets immediately in these patients.

• **Suicidal Behavior and Ideation:** Antiepileptic drugs, including pregabalin, the active ingredient in Revogab CR extended-release tablets, increase the risk of suicidal thoughts or behavior.

• **Respiratory Depression:** May occur with Revogab CR when used with concomitant CNS depressants or in the setting of underlying respiratory impairment. Monitor patients and adjust dosage as appropriate.

• **Dizziness and Somnolence:** May cause dizziness and somnolence and impair patients ability to drive or operate machinery.
• Increased seizure frequency may occur in patients with seizure disorders if pregabalin extended-release tablets is rapidly discontinued. Withdraw pregabalin extended-release tablets gradually over a minimum of 1 week.

• **Peripheral Edema:** May cause peripheral edema. Monitor patients for the development of edema when co-administering pregabalin extended-release tablets and thiazolidinedione antidiabetic agents.

Adverse Reactions/Side Effects
Most common adverse reactions reported in greater than or equal to 4% of patients treated with pregabalin extended-release tablets are dizziness, somnolence, headache, fatigue, peripheral edema, nausea, blurred vision, dry mouth, and weight gain.

Use In Specific Populations
• **Pregnancy:** May cause fetal harm. Advise of potential risk to the fetus.
• **Lactation:** Breastfeeding is not recommended.

CONTRAINDICATIONS
Revogab CR extended-release tablets are 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
Angioedema
There have been postmarketing reports of angioedema in patients during initial and chronic treatment with Revogab CR . 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 Revogab CR extended-release tablets immediately in patients with these symptoms.
Exercise caution when prescribing Revogab CR extended-release tablets 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 Reactions
There have been postmarketing reports of hypersensitivity reactions in patients shortly after initiation of treatment with Revogab CR. Adverse reactions included skin redness, blisters, hives, rash, dyspnea, and wheezing. Discontinue pregabalin extended-release tablets immediately in patients with these symptoms.

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 studies showed that pregabalin is unlikely to be involved in significant pharmacokinetic drug interactions

Pharmacodynamics
Although no pharmacokinetic interactions were seen with Revogab CR and ethanol, lorazepam, or oxycodone, additive effects on cognitive and gross motor functioning were seen when Revogab CR was co-administered with these drugs. No clinically important effects on respiration were seen in studies of Revogab CR.

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to pregabalin during pregnancy. To provide information regarding the effects of in utero exposure to Revogab CR extended-release tablets, physicians are advised to recommend that pregnant
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

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

Treatment or Management of Overdose
There is no specific antidote for overdose with pregabalin. If indicated, elimination of unabsorbed drug may be attempted by emesis or gastric lavage; observe usual precautions to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient. Contact a Certified Poison Control Center for up-to-date information on the management of overdose with pregabalin.
Pregabalin can be removed by hemodialysis. Standard hemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours).

REVOGAB CR TABLETS - CLINICAL PHARMACOLOGY
Mechanism of Action
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.

Pharmacokinetics
Revogab CR extended-release tablets has linear pharmacokinetics with dose-proportional increases in maximum plasma concentration (C max) and area under the plasma concentration-time curve (AUC) from 82.5 mg/day to 660 mg/day. Following repeated administration, steady state is achieved within approximately 48 to 72 hours.
Revogab CR extended-release tablets administered once daily following an evening meal has equivalent AUC and lower C max relative to a comparative dose of Revogab CR administered without food twice daily (Table 5). Variability in C max and AUC for Revogab CR extended-release tablets is less than or equal to 25%.

Absorption
Pregabalin is absorbed from the small intestine and proximal colon. Revogab CR extended-release tablets absorption is linear and dose proportional.
The bioavailability of Revogab CR extended-release tablets is reduced if taken on an empty stomach. The AUC is approximately 30% lower when pregabalin extended-release tablets is administered fasted relative to following an evening meal.
When Revogab CR extended-release tablets is administered following a 600 to 750 calorie (50% carbohydrates, 20% protein, 30% fat) evening meal, peak plasma concentrations occur within approximately 8 to 10 hours and AUC is approximately 93% to 97% relative to a comparative dose of Revogab CR . The rate and extent of Revogab CR extended-release tablets absorption is similar when administered following a 400 to 500 calorie, 30% fat or an 800 to 1000 calorie, 15%, 30%, or 50% fat evening meal.
When Revogab CR extended-release tablets is administered following an 800 to 1000 calorie (50% carbohydrates, 20% protein, 30% fat) morning meal, peak plasma concentrations occur within