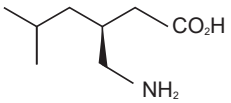
Gabica® CR
(Pregabalin)

Extended-release Tablets 82.5mg, 165mg & 330mg

DESCRIPTION
Gabica CR (Pregabalin) is an analogue of the neurotransmitter gamma-aminobutyric acid (GABA). Its chemical name is (S)-3-(aminomethyl)-5-methylhexanoic acid. Its molecular formula is $C_8H_{17}NO_2$ and the structural formula is:



Pregabalin

QUALITATIVE AND QUANTITATIVE COMPOSITION
Gabica CR (Pregabalin) is available for oral administration as:

Gabica CR Tablets 82.5mg
Each extended-release tablet contains:
Pregabalin BP…82.5mg

Gabica CR Tablets 165mg
Each extended-release tablet contains:
Pregabalin BP…165mg

Gabica CR Tablets 330mg
Each extended-release tablet contains:
Pregabalin BP… 330mg

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

Absorption
Pregabalin is absorbed from the small intestine and proximal colon. Pregabalin absorption is linear and dose proportional. The bioavailability of Pregabalin is reduced if taken on an empty stomach. The AUC is approximately 30% lower when Pregabalin administered fasted relative to following an evening meal.

Distribution
Pregabalin does not bind to plasma proteins. The apparent volume of distribution of Pregabalin following oral administration is approximately 0.5L/kg.

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.

Elimination
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 80.9mL/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.

Special Population
Geriatric Patients
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.

Patients with Renal impairment
Pregabalin clearance is nearly proportional to CLcr. Dosage reduction in patients with reduced renal function 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, treatment with Pregabalin is not recommended.

THERAPUETIC INDICATIONS
Gabica CR (Pregabalin) is indicated for the management of:
- Neuropathic pain associated with diabetic peripheral neuropathy
- Postherpetic neuralgia

DOSAGE AND ADMINISTRATION
Neuropathic Pain Associated with Diabetic Peripheral Neuropathy
Begin dosing at Gabica CR (Pregabalin) 165mg once daily and increase to Gabica CR (Pregabalin) 330mg once daily within 1 week based on individual patient response and tolerability. The maximum recommended dose of Gabica CR (Pregabalin) is 330mg once daily.

Postherpetic Neuralgia
Begin dosing at Gabica CR (Pregabalin) 165mg once daily and increase to Gabica CR (Pregabalin) 330mg once daily within 1 week based on individual patient response and tolerability.
Patients who do not experience sufficient pain relief following 2 to 4 weeks of treatment with Gabica CR (Pregabalin) 330mg once daily and who are able to tolerate Gabica CR (Pregabalin), may be treated with up to 660mg once daily. In view of the dose-dependent adverse reactions and the higher rate of treatment discontinuation due to adverse reactions, dosing above 330mg/day should be reserved only for those patients who have on-going pain and are tolerating 330mg daily. The maximum recommended dose of Gabica CR (Pregabalin) is 660mg once daily.

Special Population
Patients with Renal impairment
Use of Gabica CR (Pregabalin) Tablets is not recommended for patients with creatinine clearance (CLcr) less than 30mL/min or who are undergoing hemodialysis. Those patients should receive Gabica (Pregabalin) Capsules.
In view of dose-dependent adverse reactions and because Gabica CR (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 CLcr, as indicated in the table below. To use the dosing tables, an estimate of the patient's CLcr in mL/min is needed.

Next, refer to the Dosage and Administration to determine the recommended total daily dose based on indication, for a patient with normal renal function (CLcr greater than or equal to 60mL/min). Then refer to table below to determine the corresponding renal adjusted dose.

(For example: A patient initiating Gabica CR (Pregabalin) therapy for postherpetic neuralgia with normal renal function [CLcr greater than or equal to 60mL/min], receives a single daily dose of 165mg/day pregabalin. Therefore, a renal impaired patient with a CLcr of 50mL/min would receive a single daily dose of 82.5mg.)

Gabica CR Dosage Adjustment Based on Renal Function

Creatinine Clearance (CLcr) (mL/min)	Total Gabica CR Daily Dose (mg/day)				Dose Regimen
Greater than or equal to 60	165	330	495[a]	660[b]	Once a day
30–60	82.5	165	247.5[c]	330	Once a day
Less than 30/hemodialysis	Dose with Gabica Capsules				

a. 495mg = 3 × 165mg tablets taken once a day.
b. 660mg = 2 × 330mg tablets taken once a day.
c. 247.5mg = 3 × 82.5mg tablets taken once a day.

Conversion from Gabica Capsules to Gabica CR Tablets
When switching from Gabica Capsules to Gabica CR Tablets on the day of the switch, instruct patients to take their morning dose of Gabica Capsules as prescribed and initiate Gabica CR Tablets therapy after an evening meal.

Conversion from Gabica Capsules to Gabica CR Tablets

Gabica Capsules Total Daily Dose (dosed 2 or 3 times daily)	Gabica CR Tablets Dose (dosed once a day)
75mg/daily	82.5mg/day
150mg/daily	165mg/day
225mg/daily	247.5mg/day[a]
300mg/daily	330mg/day
450mg/daily	495mg/day[b]
600mg/daily	660mg/day[c]

a. 247.5mg = 3 × 82.5mg tablets taken once a day.
b. 495mg = 3 × 165mg tablets taken once a day.
c. 660mg = 2 × 330mg tablets taken once a day.

Administration Instruction
Gabica CR (Pregabalin) should be administered once daily after an evening meal. Gabica CR (Pregabalin) should be swallowed whole and should not be split, crushed, or chewed.

When discontinuing Gabica CR (Pregabalin), taper gradually over a minimum of 1 week.
If patients miss taking their dose of Gabica CR (Pregabalin) after an evening meal, then they should take their usual dose of Gabica CR (Pregabalin) prior to bedtime following a snack. If they miss taking the dose of Gabica CR (Pregabalin) prior to bedtime, then they should take their usual dose of Gabica CR (Pregabalin) following a morning meal. If they miss taking the dose of Gabica CR (Pregabalin) following the morning meal, then they should take their usual dose of Gabica CR (Pregabalin) at the usual time that evening following an evening meal.

ADVERSE REACTIONS
Angioedema, hypersensitivity reactions, suicidal behavior and ideation, respiratory depression, dizziness, somnolence, headache, fatigue, nausea, dry mouth, risks associated with abrupt or rapid discontinuation, peripheral edema, weight gain, ophthalmological effects, creatine kinase elevations, and decreased platelet count. Some other adverse events includes increased appetite, fever, ecchymosis, leg cramps, myalgia, myasthenia, anxiety, depersonalization, hypertonia, hypoesthesia, libido decreased, nystagmus, paresthesia, sedation, stupor, twitching, pruritis, conjunctivitis, tinitis, anorgasmia, impotence, urinary frequency, urinary incontinence, and reduced lower gastrointestinal tract function.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's Pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

CONTRAINDICATIONS
Pregabalin is contraindicated in patients with known hypersensitivity to the active substance or to any of the excipient of the product.

PRECAUTIONS
Angioedema
Angioedema has been report 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 Pregabalin immediately in patients with these symptoms.
Exercise caution when prescribing Pregabalin 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
Hypersensitivity reactions (e.g., hives, dyspnea, and wheezing) can occur. Discontinue Pregabalin immediately in these patients.

Suicidal Behavior and Ideation
Antiepileptic drugs (AEDs), including Pregabalin 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.
Inform patients, their caregivers, and families that Pregabalin can 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.

Respiratory Depression
Pregabalin is associated with serious, life-threatening, or fatal respiratory depression when co-administered with central nervous system (CNS) depressants, including opioids, or in the setting of underlying respiratory impairment.
When the decision is made to co-prescribe Pregabalin with another CNS depressant, particularly an opioid, or to prescribe Pregabalin to patients with underlying respiratory impairment, monitor patients for symptoms of respiratory depression and sedation, and consider initiating Pregabalin at a low dose.

Dizziness and Somnolence
Pregabalin 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. Concomitant use of Pregabalin with other central nervous system (CNS) depressants may exacerbate these effects.

Risks Associated with Abrupt or Rapid Discontinuation
Following abrupt or rapid discontinuation of Pregabalin, some patients reported symptoms including, insomnia, nausea, headache, anxiety, and diarrhea. Increased seizure frequency may occur in patients with seizure disorders taking Pregabalin for pain if Pregabalin is rapidly discontinued. Taper Pregabalin gradually over a minimum of 1 week rather than discontinuing the drug abruptly.

Peripheral Edema and Weight Gain
Pregabalin treatment may cause peripheral edema and/or weight gain. Higher frequencies of weight gain and peripheral edema were observed in patients taking both Pregabalin and a thiazolidinedione antidiabetic agent compared to patients taking either drug alone. As the thiazolidinedione class of antidiabetic drugs can cause weight gain and/or fluid retention, possibly exacerbating or leading to heart failure, monitor patients for the development of edema when co-administering Pregabalin and these agents. For patients with preexisting cardiac conditions this may increase the risk of heart failure.

Ophthalmological Effects
Inform patients to notify their physician if changes in vision occur. If visual disturbance persists, consider further assessment. Consider more frequent assessment for patients who are already routinely monitored for ocular conditions.

Creatine Kinase Elevations
Pregabalin treatment was associated with creatine kinase elevations. Instruct patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if these muscle symptoms are accompanied by malaise or fever. Discontinue treatment with Pregabalin if myopathy is diagnosed or suspected or if markedly elevated creatine kinase levels occur.

Decreased Platelet Count
Pregabalin treatment were associated with a decrease in platelet count. Caution is warranted.

PR Interval Prolongation
Pregabalin treatment was associated with PR interval prolongation. Caution is warranted.

Male Fertility
Pregabalin is associated with potential risk of male-mediated teratogenicity.

Pregnancy
Pregabalin may cause fetal harm. Advise patients of potential risk to the fetus.

Nursing Mothers
Small amounts of Pregabalin have been detected in the milk of lactating women and because of the potential risk of tumorigenicity, breastfeeding is not recommended during treatment with Pregabalin.

OVERDOSAGE
Signs and Symptoms
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 alone Pregabalin overdose and in combination with other CNS depressants.

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

STORAGE
Do not store above 30°C.
Protect from sunlight and moisture.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
Gabica CR (Pregabalin) Tablets 82.5mg are available in blister pack of 14's.
Gabica CR (Pregabalin) Tablets 165mg are available in blister pack of 14's.
Gabica CR (Pregabalin) Tablets 330mg are available in blister pack of 14's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:
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29-30/27, K.I.A., Karachi, Pakistan
PAK-200013502