Prescot Capsules* پری سکاٹ کیپسولز

COMPOSITION

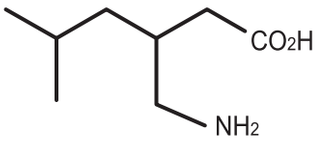
Prescot Capsules

Each capsule contains:

Pregabalin ..... 75 mg, 100 mg & 150 mg, respectively.

DESCRIPTION

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



Pregabalin is a white to off-white, crystalline solid with a pKa1 of 4.2 and a pKa2 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.

CLINICAL PHARMACOLOGY

Mechanism of Action:

Pregabalin (PRESCOT) 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 GABAa, GABAb, or benzodiazepine receptors, does not augment GABAa 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: Following oral administration of Pregabalin (PRESCOT) 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 repeated administration, steady state is achieved within 24 to 48 hours. Pregabalin can be taken with or without food.

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.

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 is 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).

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

INDICATIONS AND USAGE

Pregabalin (PRESCOT) 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.

CONTRAINDICATIONS

Pregabalin (PRESCOT) 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.

ADVERSE REACTIONS

Treatment-emergent adverse reactions reported by patients treated with Pregabalin during clinical trials are listed in the Table 1 . 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.

The adverse reactions listed may be associated with the underlying disease and/or concomitant medications.

Table 1: Adverse Events from Clinical Trial Experience

System Organ Class : Adverse Drug Reactions	
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-Barre 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

DRUG INTERACTIONS

Since Pregabalin is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans and does not bind to plasma proteins, its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions or protein binding displacement.

Specifically, there are no pharmacokinetic interactions between Pregabalin and other antiepileptic drugs. Multiple oral doses of pregabalin were co-administered with oxycodone, lorazepam, or ethanol. Although no pharmacokinetic interactions were seen, additive effects on cognitive and gross motor functioning were seen when Pregabalin was co-administered with these drugs.

USE IN SPECIFIC POPULATIONS

Pregnancy: There are no adequate and well-controlled studies with Pregabalin in pregnant women. Advise pregnant women of the potential risk to a fetus.

Lactation: Small amounts of Pregabalin have been detected in the milk of

lactating women. Because of the potential risk of tumorigenicity, breastfeeding is not recommended during treatment with Pregabalin.

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 geriatric patients and younger patients. Although the adverse reaction profile was similar between the two age groups, the following neurological adverse reactions were more frequent in patients 65 years of age or older: dizziness, vision blurred, balance disorder, tremor, confusional state, coordination abnormal, and lethargy.

Male Fertility: Inform men being treated with Pregabalin (PRESCOT) who plan to father a child of the potential risk of male- mediated teratogenicity.

DRUG ABUSE AND DEPENDENCE

Pregabalin (PRESCOT) is a Schedule V controlled substance. Pregabalin (PRESCOT) is not known to be active at receptor sites associated with drugs of abuse. In clinical studies, following abrupt or rapid discontinuation of Pregabalin, some patients reported symptoms including insomnia, nausea, headache or diarrhea, consistent with physical dependence. In the postmarketing experience, in addition to these reported symptoms there have also been reported cases of anxiety and hyperhidrosis.

WARNINGS AND PRECAUTIONS

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 PRESCOT immediately in patients with these symptoms. Exercise caution when prescribing PRESCOT to patients who have had a previous episode of angioedema. In addition, patients who are taking other drugs associated with angioedema 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 PRESCOT immediately in patients with these symptoms.

Withdrawal of Antiepileptic Drugs (AEDs): As with all AEDs, withdraw PRESCOT gradually to minimize the potential of increased seizure frequency in patients with seizure disorders. If PRESCOT is discontinued, taper the drug gradually over a minimum of 1 week.

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 PRESCOT 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.

Peripheral Edema: PRESCOT treatment may cause peripheral edema. 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 PRESCOT 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 PRESCOT in these patients.

Dizziness and Somnolence: PRESCOT may cause dizziness and somnolence. Inform patients that PRESCOT-related dizziness and somnolence may impair their ability to perform tasks such as driving or operating machinery.

Weight Gain: PRESCOT treatment may cause weight gain.

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

Ophthalmological Effects: 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: Pregabalin treatment is 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 PRESCOT if myopathy is diagnosed or suspected or if markedly elevated creatine kinase levels occur.

Decreased Platelet Count: Pregabalin treatment is associated with a decrease in platelet count & is not associated with an increase in bleeding-related adverse reactions.

PR Interval Prolongation: Pregabalin treatment is associated with PR interval prolongation.

DOSAGE AND ADMINISTRATION

PRESCOT is given orally with or without food. When discontinuing PRESCOT, taper gradually over a minimum of 1 week.

Neuropathic Pain Associated with Diabetic Peripheral Neuropathy:

The maximum recommended dose of Pregabalin (PRESCOT) 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 Pregabalin (PRESCOT) is eliminated primarily by renal excretion, adjust the dose in patients with reduced renal function. In view of the dose-dependent adverse reactions, treatment with doses above 300 mg/day is not recommended.

Postherpetic Neuralgia:

The recommended dose of Pregabalin (PRESCOT) 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. Because Pregabalin (PRESCOT) is eliminated primarily by renal excretion, adjust the dose in patients with reduced renal function.

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 Pregabalin (PRESCOT), 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.

Adjunctive Therapy for Adult Patients with Partial Onset Seizures:

Pregabalin (PRESCOT) 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, or 50 mg three times a day). Based on individual patient response and tolerability, the dose may be increased to a maximum dose of 600 mg/day. Because Pregabalin (PRESCOT) is eliminated primarily by renal excretion, adjust the dose in patients with reduced renal function. 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 (PRESCOT) with gabapentin cannot be offered.

Management of Fibromyalgia:

The recommended dose of Pregabalin (PRESCOT) 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. Because Pregabalin (PRESCOT) is eliminated primarily by renal excretion, adjust the dose in patients with reduced renal function.

Neuropathic Pain Associated with Spinal Cord Injury:

The recommended dose range of Pregabalin (PRESCOT) 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 (PRESCOT) may be treated with up to 300 mg two times a day. Because Pregabalin (PRESCOT) is eliminated primarily by renal excretion, adjust the dose in patients with reduced renal function.

Patients with Renal Impairment:

In view of dose-dependent adverse reactions and since Pregabalin (PRESCOT) 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 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:

$$\text{CLcr} = \frac{[140 - \text{Age (years)}) \times \text{Weight (kg)}]}{72 \times \text{Serum Creatinine (mg/dL)}} \quad (\times\ 0.85 \text{ for Female Patients})$$

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 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 (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.

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 (PRESCOT). 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).

STORAGE

Store in a cool, dry and dark place below 25 ºC. Keep all the medicines out of children's reach.

PRESENTATION

Prescot 75 mg, 100 mg & 150 mg are available in packing containing 14 capsules, respectively.

*Scotmann Specs.

خوراک: ڈاکٹر کی ہدایت کے مطابق۔

احتیاط: روشنی، نمی اور گرمی سے بچائیں۔

25 ڈگری سینٹی گریڈ سے کم درجہ حرارت پر محفوظ کریں۔

تمام ادویات بچوں کی پہنچ سے دور رکھیں۔

مستند ڈاکٹر کے نسخہ پر فروخت اور استعمال کریں۔

Complete Medical Information available only for doctors on request.

scotmann

Manufactured by: SCOTMANN PHARMACEUTICALS
5-D, I-10/3 Industrial Area, Islamabad-Pakistan.
www.scotmann.com