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For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory only

PREGALIN 50

(Pregabalin Capsules I.P.)

COMPOSITION

Each hard gelatin capsule contains :
Pregabalin I.P. 50 mg
Approved colours used in hard gelatin capsule shells.

DESCRIPTION

Pregabalin is chemically described as (S)-3-(aminomethyl)-5-methylhexanoic acid. The molecular formula is $C_8H_{17}NO_2$ and the molecular weight is 159.23. Pregabalin is a white to off-white, crystalline solid with a pK_{a1} of 4.2 and a pK_{a2} of 10.6. It is freely soluble in water and both basic and acidic aqueous solutions.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Pregabalin

Pregabalin binds with high affinity to the alpha$_2$ - delta site (an auxiliary subunit of voltage-gated calcium channels) in central nervous system tissues. Animal studies suggest that binding to the alpha$_2$ - delta subunit may be involved in pregabalin's antinociceptive and antiseizure effects in animal models. *In vitro,* pregabalin reduces the calcium dependent release of several neurotransmitters, possibly by modulation of calcium channel function.

Although pregabalin is a structural derivative of the inhibitory neurotransmitter gammaaminobutyric 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 nor-epinephrine reuptake.

Pharmacokinetics

Pregabalin

Pregabalin is well absorbed after oral administration, is eliminated largely by renal excretion, and has an elimination half-life of about 6 hours. Following oral administration of pregabalin capsules under fasting conditions, peak plasma concentrations occur within 1.5 hours. Pregabalin oral bioavailability is ‡ 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. 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.

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. A mean elimination half-life of pregabalin is 6.3 hours in subjects with normal renal function. Pregabalin elimination is nearly proportional to creatinine clearance (CLcr).

INDICATIONS AND USAGE

Pregabalin is indicated for management of neuropathic pain.

CONTRAINDICATIONS

This capsule is contraindicated in patients with known hypersensitivity to any of its components.

WARNINGS

The use of this capsule to treat any medical condition requires medical supervision.

Withdrawal of rapid discontinuation

Pregabalin should be withdrawn gradually to minimize the potential of increased seizure frequency in patients with seizure disorders and in some patients reported symptoms including insomnia, nausea, headache and diarrhea. If pregabalin is discontinued this should be done gradually over a minimum of 1 week.

Tumorogenic 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.

PRECAUTIONS

Pregabalin

Dizziness and somnolence

Pregabalin causes dizziness and somnolence. Patients should be informed that pregabalin-related dizziness and somnolence may impair their ability to perform tasks such as driving or operating machinery.

Ophthalmological Effects

Patients should be informed that if changes in vision occur, they should notify their physician. If visual disturbance persists, further assessment should be considered. More frequent assessment should be considered for patients who are already routinely monitored for ocular conditions.

Weight Gain

Pregabalin treatment is reported to cause weight gain. While the effects of pregabalin-associated weight gain on glycemic control have not been systematically assessed, pregabalin treatment did not appear to be associated with loss of glycemic control (as measured by HbA_{1C}).

Peripheral Edema

Pregabalin treatment is reported to cause edema, primarily described as peripheral edema. 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, care should be taken when coadministering pregabalin 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, pregabalin should be used with caution in these patients.

Creatine kinase elevations

Pregabalin treatment is associated with creatine kinase elevations. Prescribers should instruct patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if these muscle symptoms are accompanied by malaise or fever. Pregabalin treatment should be discontinued if myopathy is diagnosed or suspected or if markedly elevated creatine kinase levels occur.

Laboratory changes

Decreased platelet count

Pregabalin treatment is associated with a decrease in platelet count. However in controlled clinical studies, pregabalin was not associated with an increase in bleeding related adverse events.

ECG changes

PR interval prolongation

Pregabalin treatment is known to be associated with mild PR interval prolongation. 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No evidence of carcinogenicity was seen in animal studies following dietary administration of pregabalin for two years at doses that were associated with plasma exposures in males and females up to approximately 14 and 24 times, respectively, human exposure at the maximum recommended dose (MRD).

Mutagenesis

Pregabalin was not mutagenic in bacteria or in mammalian cells *in vitro,* was not clastogenic in mammalian systems *in vitro* and *in vivo,* and did not induce unscheduled DNA synthesis in mouse or rat hepatocytes.

Impairment of Fertility

In fertility studies in which male rats were orally administered pregabalin (50 to 2500 mg/kg) prior to and during mating with untreated females, a number of adverse reproductive and developmental effects observed included decreased sperm counts and sperm motility, increased sperm abnormalities, reduced fertility, increased preimplantation embryo loss, decreased litter size, decreased fetal body weights, and an increased incidence of fetal abnormalities. Effects on sperm and fertility parameters were reversible in studies of this duration (3-4 months).

Human Data

In a double-blind, placebo-controlled clinical trial to assess the effect of pregabalin on sperm motility, 30 healthy male subjects were exposed to pregabalin at a dose of 600 mg/day. After 3 months of treatment (one complete sperm cycle), the difference between placebo- and pregabalin-treated subjects in mean percent sperm with normal motility was <4% and neither group had a mean change from baseline of more than 2%. Effects on other male reproductive parameters in humans have not been adequately studied.

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Pregabalin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effects of pregabalin on labor and delivery in pregnant women are unknown.

Use in Nursing Mothers

It is not known if pregabalin is excreted in human milk; it is, however, present in the milk of rats. Because many drugs are excreted in human milk, and because of the potential for tumorigenicity shown for pregabalin in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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 elderly patients and younger patients in controlled studies. Even though the incidence of adverse events did not show age related increase, greater sensitivity of some older individuals cannot be ruled out.

Renal Impairment

Pregabalin is known to be substantially excreted by the kidney, and the risk of toxic reactions to pregabalin may be greater in patients with impaired renal function. The dose should be adjusted for elderly patients with renal impairment.

ADVERSE REACTIONS

Most Common Adverse Events

In patients with neuropathic pain associated with diabetic peripheral neuropathy, the most common reasons for discontinuation due to adverse events were dizziness, somnolence, asthenia, confusion, and peripheral edema. In patients with postherpetic neuralgia the most common reasons for discontinuation due to adverse events were dizziness, somnolence, confusion, peripheral edema, asthenia, ataxia, and abnormal gait. Adverse events due to pregabalin combinations, regardless of causality, occurring in ‡1% of patients with neuropathic pain associated with diabetic neuropathy. Majority of the adverse events is with an intensity of Mild or Moderate

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, in coordination, amnesia, speech disorder
Respiratory system - Bronchitis
Special senses - Blurry vision, diplopia, abnormal vision, eye Disorder
Urogenital System - Urinary Incontinence

Other Adverse Events for which drug cause is remote and do not have a substantial probability of being acutely life threatening.

Body as a whole: *Frequent* - abdominal pain, allergic reaction, fever, *Infrequent* - abscess, cellulitis, chills, malaise, neck rigidity, overdose, pelvic pain, photosensitivity reaction, suicide attempt, *Rare-* anaphylactoid reaction, ascites, granuloma, hangover effect, intentional injury, retroperitoneal fibrosis, shock, suicide.
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.
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-* generalized spasm.
Nervous system: *Frequent-* anxiety, depersonalization, hypertonia, hypesthesia, libido decreased, nystagmus, paresthesia, 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, psychotic depression, schizophrenic reaction, 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, petechial rash, purpuric rash, pustular rash, skin atrophy, skin necrosis, skin nodule, stevens-johnson syndrome, subcutaneous.
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, *Rare-* acute kidney failure, balanitis, bladder neoplasm, cervicitis, dyspareunia, epididymitis, female lactation, glomerulitis.

DOSAGE AND ADMINISTRATION

Neuropathic pain associated with diabetic peripheral neuropathy:
Pregabalin dosing beginning at 50mg three times a day (150mg/day) and may be increased to 300mg/day within 1 week based on efficacy and tolerability in patients with creatinine clearance of at least 60ml/min.

Patients with Renal Impairment

In view of dose-dependent adverse events and since pregabalin is eliminated primarily by renal excretion, the dose should be adjusted in patients with reduced renal function. Dosage adjustment in patients with renal impairment should be based on Cl_{cr}, as indicated in the table given below. To use this dosing table, an estimate of the patient's Cl_{cr} in ml/min is needed. Cl_{cr} in ml/min may be estimated from serum creatinine (mg/dL) determination using the Cockcroft and Gault equation:

$$Cl_{cr} = \frac{[140 - \text{age (years)}] \times \text{body weight (kgs)}}{72 \times \text{serum creatinine (mg/dl)}}$$

To account for females, Cl_{cr} determined from above equation should be multiplied by 0.85. For patients undergoing hemodialysis, pregabalin daily dose should be adjusted based on renal function. In addition to the daily dose adjustment, a supplemental dose should be given immediately following every 4-hour hemodialysis treatment as given in the table below.

Pregabalin Dosage Adjustment Based on Renal Function

Creatinine clearance (ml/min)	Total Pregabalin Daily Dose (mg/day)[a]			Dose Regimen
‡ 60	150	300	600	BID or TID
30-60	75	150	300	BID or TID
15-30	25-50	75	150	QD or BID
<15	25	25-50	75	QD

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

OVERDOSE

Pregabalin

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. In clinical studies, some patients took as much as 2400 mg/day. The types of adverse events experienced by patients exposed to higher doses (‡ 900 mg) were not clinically different from those of patients administered recommended doses of pregabalin.

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. 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).

EXPIRY DATE

Do not use later than the date of expiry.

STORAGE

Store at a temperature not exceeding 30^{o}C, protected from moisture.
Keep out of reach of children

PRESENTATION

Pregalin 50 is available in blister pack of 10 capsules.

torrent

Manufactured by :
TORRENT PHARMACEUTICALS LTD.
Vill. Bhud & Makhnu Majra, Baddi-173 205,
Teh. Nalagarh, Dist. Solan (H.P.), INDIA.