xxxxxxx-5343

PREGABALIN

PREGEB 75
PREGEB 150
75 mg & 150 mg Capsule
Anticonvulsant

FORMULATION:
Each capsule contains:
Pregabalin…… 75 mg / 150 mg
PRODUCT DESCRIPTION
Pregabalin (Pregeb 75) 75 mg Capsule is a size '4', hard gelatin capsule having reddish brown opaque cap and white opaque body, imprinted '1360' on cap and "75" on body with black ink containing white to off-white powder.
Pregabalin (Pregeb 150) 150 mg Capsule is a size '1', hard gelatin capsule having white opaque cap and white opaque body, imprinted '1362' on cap and '150' on body with black ink containing white to off white powder.
PHARMACODYNAMICS:
Mechanism of action
Pregabalin binds to the α2δ (alpha2delta) subunit of the voltage-dependent calcium channel in the central nervous system. Pregabalin decreases the release of neurotransmitters including glutamate, norepinephrine, substance P and calcitonin gene-related peptide. However, unlike anxiolytic compounds (e.g., benzodiazepines) which exert their therapeutic effects through binding to gamma-aminobutyric acid receptor A (GABAA), gamma-aminobutyric acid receptor B (GABAB), and benzodiazepine receptors, Pregabalin neither binds directly to these receptors nor augments GABAA currents or affects GABA metabolism.
PHARMACOKINETICS:
Absorption: Pregabalin is rapidly absorbed when administered in the fasted state, with peak plasma concentrations occurring within 1 hour following both single and multiple dose administration. Pregabalin oral bioavailability is estimated to be ≥90% and is independent of dose. Following repeated administration, steady state is achieved within 24 to 48 hours. The rate of pregabalin absorption is decreased when given with food resulting in a decrease in Cmax by approximately 25-30% and a delay in t max to approximately 2.5 hours. However, administration of pregabalin with food has no clinically significant effect on the extent of Pregabalin absorption.
Distribution: In preclinical studies, pregabalin has been shown to cross the blood brain barrier in mice, rats, and monkeys. Pregabalin has been shown to cross the placenta in rats and is present in the milk of lactating rats. In humans, the apparent volume of distribution of pregabalin following oral administration is approximately 0.56 l/kg. Pregabalin is not bound to plasma proteins.
Biotransformation: Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabelled pregabalin, approximately 98% of the radioactivity recovered in the urine was 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, there was no indication of racemisation of pregabalin S-enantiomer to the R-enantiomer.
Elimination: Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. Pregabalin mean elimination half-life is 6.3 hours. Pregabalin plasma clearance and renal clearance are directly proportional to creatinine clearance. Dose adjustment in patients with reduced renal function or undergoing haemodialysis is necessary
Linearity / non-linearity: Pregabalin pharmacokinetics are linear over the recommended daily dose range. Inter-subject pharmacokinetic variability for pregabalin is low (<20%). Multiple dose pharmacokinetics are predictable from single-dose data. Therefore, there is no need for routine monitoring of plasma concentrations of pregabalin.
Pharmacokinetics in special patient groups:
Gender: Clinical trials indicate that gender does not have a clinically significant influence on the plasma concentrations of pregabalin.
Renal impairment: Pregabalin clearance is directly proportional to creatinine clearance. In addition, pregabalin is effectively removed from plasma by haemodialysis (following a 4 hour haemodialysis treatment plasma pregabalin concentrations are reduced by approximately 50%). Because renal elimination is the major elimination pathway, dose reduction in patients with renal impairment and dose supplementation following haemodialysis is necessary
Hepatic impairment: No specific pharmacokinetic studies were carried out in patients with impaired liver function. Since pregabalin does not undergo significant metabolism and is excreted predominantly as unchanged drug in the urine, impaired liver function would not be expected to significantly alter pregabalin plasma concentrations.
Elderly (over 65 years of age): Pregabalin clearance tends to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with decreases in creatinine clearance associated with increasing age. Reduction of pregabalin dose may be required in patients who have age related compromised renal function.
INDICATIONS:
Pregabalin is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalization.
DOSAGE AND ADMINISTRATION:
The dose range is 150 to 600mg per day given in either two or three divided doses.
Epilepsy: Pregabalin treatment can be started with a dose of 150mg per day given as two or three divided doses. Based on individual patient response and tolerability, the dose may be increased to 300mg per day after 1 week. The maximum dose of 600mg per day may be achieved after an additional week.
Discontinuation of pregabalin: In accordance with current clinical practice, if pregabalin has to be discontinued it is recommended this should be done gradually over a minimum of 1 week independent of the indication.
Special populations:
Patients with renal impairment: Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. As pregabalin clearance is directly proportional to creatinine clearance, dose reduction in patients with compromised renal function must be individualized according to creatinine clearance (CLcr), as indicated in Table 1 determined using the following formula:

$$\text{CLcr (ml/min)} = \left[\frac{1.23 \times [140\text{-age (years)}] \times \text{weight (kg)}}{\text{serum creatinine } (\mu\text{mol/l})}\right] (\times 0.85 \text{ for female patients})$$

Pregabalin is removed effectively from plasma by haemodialysis (50% of drug in 4 hours). For patients receiving haemodialysis, the pregabalin daily dose should be adjusted based on renal function. In addition to the daily dose, a supplementary dose should be given immediately following every 4-hour haemodialysis treatment (see Table 1)
Table1. Pregabalin dose adjustment based on renal function

Creatinine Clearance (CLcr) (mL/min)	Total Pregabalin Daily Dose*		Dosage Regimen
	Starting dose (mg/ml)	Maximum dose (mg/ml)	
60	150	600	BID or TID
30 - <60	75	300	BID or TID
15 - <30	25-50	150	Once Daily or BID
<15	25	75	Once Daily
Supplementary dosage following haemodialysis (mg)			
	25	100	Single dose+

TID = Three divided doses
BID = Two divided doses
* Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose
+ Supplementary dose is a single additional dose
Use in patients with hepatic impairment: No dose adjustment is required for patients with hepatic impairment.
Paediatric population: The safety and efficacy of Pregabalin in children below the age of 12 years and in adolescents (12-17 years of age) have not been established. No data are available.
Use in the elderly (over 65 years of age): Elderly patients may require a dose reduction of pregabalin due to a decreased renal function.
METHOD OF ADMINISTRATION:
Pregabalin capsule may be taken with or without food.
CONTRAINDICATIONS:
Hypersensitivity to the active substance or to any of the excipients.
WARNINGS & 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 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.
Peripheral Edema: Pregabalin 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.
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, exercise caution when co-administering Pregabalin and these agents.
Diabetic patients: In accordance with current clinical practice, some diabetic patients who gain weight on pregabalin treatment may need to adjust hypoglycaemic medicinal products.
Hypersensitivity reactions: There have been reports in the postmarketing experience of hypersensitivity reactions, including cases of angioedema. Pregabalin should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper airway swelling occur. Dizziness, somnolence, loss of consciousness, confusion, and mental impairment.
Pregabalin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in the elderly population. There have also been post-marketing reports of loss of consciousness, confusion and mental impairment. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medicinal product.
Vision-related effects: In controlled trials, a higher proportion of patients treated with pregabalin reported blurred vision than did patients treated with placebo which resolved in a majority of cases with continued dosing. In the clinical studies where ophthalmologic testing was conducted, the incidence of visual acuity reduction and visual field changes was greater in pregabalin-treated patients than in placebo-treated patients; the incidence of fundoscopic changes was greater in placebo-treated patients
In the post-marketing experience, visual adverse reactions have also been reported, including loss of vision, visual blurring or other changes of visual acuity, many of which were transient. Discontinuation of pregabalin may result in resolution or improvement of these visual symptoms.
Renal failure: Cases of renal failure have been reported and in some cases discontinuation of pregabalin did show reversibility of this adverse reaction.
Withdrawal of concomitant antiepileptic medicinal products: There are insufficient data for the withdrawal of concomitant antiepileptic medicinal products, once seizure control with pregabalin in the add-on situation has been reached, in order to reach monotherapy on pregabalin.
Withdrawal symptoms: After discontinuation of short-term and long-term treatment with pregabalin withdrawal symptoms have been observed in some patients. The following events have been mentioned: insomnia, headache, nausea, anxiety, diarrhea, flu syndrome, nervousness, depression, pain, convulsion, hyperhydrosis and dizziness. The patient should be informed about this at the start of the treatment.

Convulsions, including status epilepticus and grand mal convulsions, may occur during pregabalin use or shortly after discontinuing pregabalin.
Concerning discontinuation of long-term treatment of pregabalin there are no data of the incidence and severity of withdrawal symptoms in relation to duration of use and dose of pregabalin.
Congestive heart failure: There have been post-marketing reports of congestive heart failure in some patients receiving pregabalin. These reactions are mostly seen in elderly cardiovascular compromised patients during pregabalin treatment. Pregabalin should be used with caution in these patients. Discontinuation of pregabalin may resolve the reaction.
Suicidal ideation and behavior: Suicidal ideation and behavior have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomized placebo controlled studies of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behavior. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for pregabalin.
Therefore, patients should be monitored for signs of suicidal ideation and behaviors and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behavior emerge.
Reduced lower gastrointestinal tract function: There are post-marketing 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. When pregabalin and opioids will be used in combination, measures to prevent constipation may be considered (especially in female patients and elderly).
Abuse potential: Cases of abuse have been reported. Caution should be exercised in patients with a history of substance abuse and the patient should be monitored for symptoms of pregabalin abuse.
Encephalopathy: Cases of encephalopathy have been reported, mostly in patients with underlying conditions that may precipitate encephalopathy
DRUG INTERACTIONS:
Since pregabalin is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (<2% of a dose recovered in urine as metabolites), does not inhibit drug metabolism in vitro, and is not bound to plasma proteins, it is unlikely to produce, or be subject to, pharmacokinetic interactions.
In vivo studies and population pharmacokinetic analysis
Accordingly, in in-vivo studies no clinically relevant pharmacokinetic interactions were observed between pregabalin and phenytoin, carbamazepine, valproic acid, lamotrigine, gabapentin, lorazepam, oxycodone or ethanol. Population pharmacokinetic analysis indicated that oral antidiabetics, diuretics, insulin, phenobarbital, tiagabine and topiramate had no clinically significant effect on pregabalin clearance.
Oral contraceptives, norethisterone and/or ethinyl oestradiol
Co-administration of pregabalin with the oral contraceptives norethisterone and/or ethinyl oestradiol does not influence the steady-state pharmacokinetics of either substance.
Ethanol, lorazepam, oxycodone
Pregabalin may potentiate the effects of ethanol and lorazepam. In controlled clinical trials, multiple oral doses of pregabalin co-administered with oxycodone, lorazepam, or ethanol did not result in clinically important effects on respiration. In the postmarketing experience, there are reports of respiratory failure and coma in patients taking pregabalin and other CNS depressant medicinal products. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone..
Interactions and the elderly
No specific pharmacodynamic interaction studies were conducted in elderly volunteers. Interaction studies have only been performed in adults.
PREGNANCY AND LACTATION:
Pregnancy: There are no adequate data from the use of pregabalin in pregnant women.
Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.
Pregabalin should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the fetus).
Breast-feeding: It is not known if pregabalin is excreted in the breast milk of humans; however, it is present in the milk of rats. Therefore, breast-feeding is not recommended during treatment with pregabalin.
Fertility: There are no clinical data on the effects of pregabalin on female fertility.
ADVERSE EFFECTS:
Most Common: dizziness, somnolence
Body as a Whole: asthenia, accidental injury, back pain, chest pain, face edema, infection, headache, pain, flu syndrome
Digestive: dry mouth, constipation, flatulence, vomiting, increased appetite, abnormal distention
General Disorders and Administrative Site Conditions: fatigue, peripheral edema, chest pain, feeling abnormal, edema, feeling drunk
Infections and Infestations: sinusitis, nasopharyngitis
Metabolic and Nutritional: peripheral edema, weight gain, edema, hypoglycemia
Musculoskeletal and Connective Tissue Disorders: myasthenia, arthralgia, muscle spasms, back pain, pain in extremity, muscular weakness, neck pain, joint swelling
Nervous: dizziness, somnolence, neuropathy, ataxia, vertigo, confusion, euphoria, incoordination, thinking abnormal, tremor, abnormal gait, amnesia, nervousness, speech disorder, twitching, confusion, myoclonus, disturbance in attention, memory impairment, hypoesthesia, lethargy, paresthesia
Psychiatric: euphoric mood, confusional state, anxiety, disorientation, depression, insomnia
Respiratory, Thoracic, and Mediastinal Disorders: dyspnea, bronchitis, pharyngolaryngeal pain
Skin and Subcutaneous Tissue Disorders: decubitus ulcer
Special Senses: blurred vision, abnormal vision, diplopia, eye disorder, vertigo
Urogenital: urinary incontinence
Vascular: hypertension, hypotension
Other:
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
MusculoskeletalSystem - 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, Psychoticdepression, Schizophrenic reaction, Sleep disorder, Torticollis, Trismus
Respiratory System- Rare: Apnea, Atelectasis, Bronchiolitis, Hiccup, Laryngismus, Lung edema,Lung fibrosis, Yawn
Skin 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 accomodation, 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, Opthalmoplegia, 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
Post Marketing Experience:
Nervous System Disorders - Headache
Gastrointestinal Disorders - Nausea, Diarrhea
Reproductive System and Breast Disorders - Gynecomastia, Breast Enlargement

"For suspected adverse drug reaction, report to FDA: www.fda.gov.ph or to TORRENT: www.torrentpharma.com".
Patient to seek medical attention immediately at the first sign of any adverse drug reaction shall appear.
OVERDOSAGE AND TREATMENT:
In overdoses up to 15 g, no unexpected adverse reactions were reported.
In the post-marketing experience, the most commonly reported adverse reactions observed when pregabalin was taken in overdose included somnolence, confusional state,
agitation, and restlessness.
Treatment of pregabalin overdose should include general supportive measures and may include haemodialysis if necessary.
STORAGE CONDITION:
Store at temperatures not exceeding 30°C.
CAUTION:
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.
AVAILABILITY:
Pregabalin (Pregeb 75) 75 mg Capsule - Alu-Alu Blister Pack of 10's (Box of 30's) - DR-XY44845
Pregabalin (Pregeb 150) 150 mg Capsule - Alu-Alu Blister Pack of 10's (Box of 30's) - DR-XY44846
DATE OF FIRST AUTHORIZATION:
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torrent PHARMA

Manufactured by :
TORRENT PHARMACEUTICALS LTD.
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Makati City, PHILIPPINES

PRODUCT NAME	:	Pregeb				Date	
ITEM / PACK	:	Insert	COUNTRY : Philippines	LOCATION : INDRAD	Supersedes A/W No.:		
DESIGN STYLE	:	Front/Back	NO. OF COLORS: 1	REMARK :		Signature	Name
CODE	:	xxxxxxx-5343	PANTONE SHADE NOS.:	SUBSTRATE :		Department	
DIMENSIONS (MM)	:	150 x 370		Activities		Prepared By	Pkg.Dev
ART WORK SIZE	:	S/S				Reviewed By	Pkg.Dev
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