3010596

PREGABALIN FUNXION®

50 mg, 75 mg and 1 50 mg CAPSULE

ANTICONVULSANT

FORMULATION

Each capsule contains:

Pregabalin……50 mg, 75 mg, or 150 mg

PHARMACOLOGIC CATEGORY

Anticonvulsant

PRODUCT DESCRIPTIONS

50 mg Capsule: Hard gelatin capsule with green cap and yellow body.
75 mg Capsule: Hard gelatin capsule with blue cap and white body.
150 mg Capsule: Hard gelatin capsule with maroon cap and dark yellow body.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Pregabalin is an anticonvulsant that is structurally related to the inhibitory central nervous system (CNS) neurotransmitter gamma aminobutyric acid (GABA). Although pregabalin was developed as a structural analog of GABA, the drug does not bind directly to $GABA_A$, $GABA_B$, or benzodiazepine receptors; does not augment $GABA_A$ responses in cultured neurons; and does not alter brain concentrations of GABA in rats or affect 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 binds with high affinity to the α_2-δ site (an auxiliary subunit of voltage-gated calcium channels) in CNS tissues. Although the exact mechanism of action of pregabalin has not been elucidated, binding to the α_2-δ subunit may be involved in pregabalin's anticonvulsant effect. *In vitro*, pregabalin reduces the calcium-dependent release of several neurotransmitters, including glutamate, norepinephrine, calcitonin gene-related peptide, and substance P, possibly by modulation of calcium channel function.

PHARMACOKINETICS

Pregabalin is rapidly absorbed when administered in the fasted state, with peak plasma concentrations occurring within one hour after both single and multiple dose administration. Pregabalin oral bioavailability is estimated to be ≥90% and is independent of dose. Maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) values increase proportionality after single- and multiple-dose administration. After 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 C_{max} by approximately 25 to 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 bioavailability.

At clinical doses of 150 to 600 mg per day, the average steady-state plasma pregabalin concentrations were approximately 1.5 and 6 g/mL, respectively. 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.

The apparent volume of distribution of pregabalin after oral administration is approximately 0.56 L/kg. Pregabalin is not bound to plasma proteins. Pregabalin is a substrate for system L transporter which is responsible for the transport of large amino acids across the blood brain barrier. In animal models, pregabalin has been shown to cross the blood brain barrier.

Pregabalin undergoes negligible metabolism in human. After 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 racemization of pregabalin S-enantiomer to the R-enantiomer.

Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. Renal clearance (CL_r) derived from Phase I studies was 73 mL/min. Pregabalin mean elimination half-life is 6.3 hours. Pregabalin plasma clearance and renal clearance are directly proportional to creatinine clearance.

Special Population:

Renal impairment: Pregabalin clearance is directly proportional to creatinine clearance. In addition, pregabalin is effectively removed from plasma by hemodialysis (after a four hour hemodialysis treatment plasma pregabalin concentrations are reduced by approximately 50%). Because renal elimination is the major elimination pathway, dosage reduction in patients with renal impairment and dosage supplementation after hemodialysis is necessary.

Hepatic impairment: 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 (65 years and older): 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

- Adjunctive therapy for adult patients with partial onset seizures
- Treatment of generalized anxiety disorder (GAD) in adults

DOSAGE AND ADMINISTRATION

Pregabalin can be taken with or without food. When discontinuing pregabalin, taper gradually over a minimum of one week independent of the indication.

Recommended Dose Range: 150 to 600 mg per day given in either two or three divided doses.

Epilepsy

Initial Dose: 150 mg per day given as two or three divided doses;
Based on individual patient response and tolerability, the dose may be increased to 300 mg per day after one week.

Maximum Dose: 600 mg per day may be achieved after an additional week.
It is not necessary to monitor plasma pregabalin concentrations to optimize pregabalin therapy. Pregabalin does not alter the plasma concentrations of other commonly used AEDs. Similarly, commonly used AEDs do not alter plasma concentrations of pregabalin.

Generalized Anxiety Disorder

Recommended Dose Range: 150 to 600 mg per day given as two or three divided doses; The need for treatment should be reassessed regularly.

Initial Dose: 150 mg per day;
Based on individual patient response and tolerability, the dose may be increased to 300 mg per day after one week. After an additional week the dose may be increased to 450 mg per day.

Maximum Dose: 600 mg per day may be achieved after an additional week.

Special Population:

Renal Impairment: For patients receiving hemodialysis, the pregabalin daily dose should be adjusted based on renal function. In addition to the daily dose, a supplementary dose should be given immediately after every 4-hour hemodialysis treatment.

Pregabalin Dosage Adjustment Based on Renal Function

Creatinine clearance (CL_{cr})(mL/min)	Total Pregabalin Daily Dose*		Dose regimen
	Starting Dose (mg/day)	Maximum Dose (mg/day)	
≥ 60	150	600	BID
30 to 60	75	300	QD or BID
15 to 30	25 to 50	150	QD or BID
<15	25	75	QD
Supplementary dosage after hemodialysis (mg)			
	25	100	Single 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

BID: Two divided doses
QD: Single daily dose

Hepatic Impairment: No dosage adjustment is required for patients with hepatic impairment.

Elderly (65 years and older): No dosage adjustment is necessary for elderly patients unless their renal function is compromised.

Or, as prescribed by a physician.

CONTRAINDICATION

Known hypersensitivity to pregabalin or any ingredient in the formulation.

WARNINGS AND PRECAUTIONS

Angioedema

There have been postmarketing reports of angioedema in patients, some without reported previous history/episode, during initial/acute and chronic treatment with pregabalin. Specific symptoms included swelling of the face, mouth (tongue, lips, and gums), and neck, throat, and larynx/upper airway. There were reports of life-threatening angioedema with respiratory compromise requiring emergency treatment. Some of these patients did not have reported previous history/episode of angioedema. Discontinue pregabalin immediately in patients with these symptoms.

Exercise caution when prescribing pregabalin to patients who have had a previous episode of angioedema. Patients who are taking other drugs associated with angioedema (e.g., angiotensin converting enzyme inhibitors or ACE-inhibitors) 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 pregabalin immediately in patients with these symptoms.

Serious Skin Reactions

There have been very rare postmarketing reports of serious cutaneous reactions, including Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), dermatitis exfoliative, bullous skin reactions, and erythema multiforme in patients treated with pregabalin. Most of the reports were in patients taking concomitant drugs also associated with the potential development of these serious skin reactions. Therefore, in most cases, causality in relation to pregabalin could not be clearly established. Patients should be advised that if they experience a skin rash, they should discontinue pregabalin treatment and contact their physician for assessment and advice.

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.

Anyone considering prescribing pregabalin or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Inform patients, their caregivers, and families that pregabalin 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. Report behaviors of concern immediately to healthcare providers.

Withdrawal Symptoms

After abrupt or rapid discontinuation of pregabalin, the following events have been reported: insomnia, headache, nausea, anxiety, diarrhea, flu syndrome, nervousness, depression, pain, convulsion, hyperhidrosis, and dizziness, suggestive of physical dependence. 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, data suggest that the incidence and severity of withdrawal of symptoms may be dose-related.

As with all AEDs, withdraw pregabalin gradually to minimize the potential of increased seizure frequency in patients with seizure disorders. If pregabalin is discontinued, taper the drug gradually over a minimum of one week.

Dizziness and Somnolence

Pregabalin causes dizziness and somnolence. Inform patients that pregabalin-related dizziness and somnolence may impair their ability to perform tasks such as driving or operating machinery. There have also been reports of loss of consciousness, confusion, and mental impairment.

Substance Misuse, Abuse and Dependence

There have been postmarketing reports of substance misuse and abuse with pregabalin. As with any CNS drug, patients should be carefully evaluated for a history of substance abuse and observed for signs of pregabalin misuse or abuse (e.g., development of tolerance, increase in dose, drug-seeking behavior).

Monotherapy for Seizure Control

In patients where pregabalin was used as add-on therapy, there are insufficient data on seizure control when concomitant AEDs were withdrawn and pregabalin was used as monotherapy.

Encephalopathy

Cases of encephalopathy have been reported, mostly in patients with underlying conditions that may precipitate encephalopathy. Some cases were reported in patients with a history of kidney or liver disease. Since there have been rare reports of renal failure with pregabalin, specific caution should be exercised when prescribing pregabalin to the elderly with age-related compromised renal function and patients with kidney disease or risk factors for renal failure.

Treatment of central neuropathic pain due to spinal cord injury

In general, CNS adverse reactions, particularly somnolence, was increased in the treatment of central neuropathic pain due to spinal cord injury. This may be attributed to an additive effect due to concomitant drugs (e.g., anti-spasticity agents) needed for this condition. This should be considered when prescribing pregabalin in this condition.

Peripheral Edema

In controlled studies, peripheral edema occurred more frequently in patients treated with pregabalin than in patients treated with placebo. Peripheral edema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function.

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 for a neuropathic indication. Pregabalin should be used with caution in these patients. Discontinuation of pregabalin may resolve the reaction.

Weight Gain

Pregabalin treatment may cause weight gain. Pregabalin associated weight gain was related to dose and length of exposure, but did not appear to be associated with baseline body mass index, gender or age. Weight gain was not limited to patients with edema and was not necessarily due to edema-related events. Although weight gain was not associated with clinically important changes in blood pressure in short-term controlled studies, the long-term cardiovascular effects of pregabalin-associated weight gain are unknown. While the effects of pregabalin-associated weight gain on glycemic control have been systematically assessed, in controlled and longer-term open label studies with diabetic patients, pregabalin treatment did not appear to be associated with loss of glycemic control. In accordance with current clinical practice, some diabetic patients who gain weight on pregabalin treatment may need to adjust hypoglycemic drugs.

Gastrointestinal Effect

There have been postmarketing reports of events related to reduce lower gastrointestinal tract function (e.g., intestinal obstruction, paralytic ileus, constipation) in patients, some without reported previous history/episode, during initial/acute and chronic treatment with pregabalin, primarily in combination with other drugs that have the potential to produce constipation, such as opioid analgesics. Some of these events were considered serious and required hospitalization. When pregabalin and opioids will be used in combination, measures to prevent constipation may be considered, particularly in female patients and the elderly as they may be at increased risk of experiencing lower gastrointestinal related events.

Renal Failure

There are reports of patients, with or without previous history, experiencing renal failure while receiving pregabalin alone or in combination with other drugs. Discontinuation of pregabalin should be considered as it has shown reversibility of this event in some cases. Caution is advised when prescribing pregabalin to the elderly or those with any degree of renal impairment.

Creatine Kinase Elevations

Treatment with pregabalin was associated with creatine kinase elevations. In pre-marketing studies, some patients had events reported as rhadbomyolysis; however the relationship between these myopathy events and pregabalin is not completely understood. Pregabalin should be discontinued if myopathy is diagnosed or suspected or if markedly elevated creatine kinase levels occur.

Ophthalmological Effects

In controlled studies, a higher proportion of patients treated with pregabalin reported blurred vision than did patients treated with placebo. In the majority of cases, blurred vision resolved with continued dosing. If blurred vision persists, further assessment should be considered.

In postmarketing 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.

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

EFFECTS ON ABILITY TO DRIVE AND USE MACHINE

Pregabalin may have minor or moderate influence on the ability to drive and use machines. Pregabalin may cause dizziness and somnolence and therefore may have an influence on the ability to drive or use machines. Patients are advised not to drive, operate complex machinery or engage in other potentially hazardous activities until it is known whether this medication affects their ability to perform these activities.

INTERACTIONS WITH OTHER MEDICAMENTS

- **Drugs affecting hepatic microsomal enzymes:** *In vitro* drug metabolism showed that pregabalin at concentrations which were, in general, 10-fold greater than observed in Phase 2/3 clinical trials, does not inhibit human CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6,CYP2E1, and CYP3A4 enzyme systems.
- **Anticonvulsants:** *In vitro* and *in vivo* studies showed that pregabalin is unlikely to be involved in significant pharmacokinetic drugs interactions. There are no clinically significant pharmacokinetic interactions between pregabalin and the following: carbamazepine, valproic acid, lamotrigine, phenytoin, phenobarbital, and topiramate. Important pharmacokinetic interactions would also not be expected to occur between pregabalin and commonly used AEDs.
- **ACE inhibitors:** Potential pharmacologic interaction with ACE inhibitors (e.g., increased risk of developing angioedema).
- **Tiagabine:** In patients with partial seizures, tiagabine had no clinically significant effect on pregabalin clearance.
- **Gabapentin:** Gabapentin pharmacokinetics after single and multiple dose administration were unaltered by pregabalin coadministration. The rate of pregabalin's absorption was reduced by approximately 26% (single dose administration) and 18% (multiple dose administration) based on lower C_{max} values; however, the extent of pregabalin absorption was unaffected by gabapentin coadministration.
- **Oral contraceptives:** Concomitant use with pregabalin had no effect on the steady state pharmacokinetics of norethindrone and ethinyl estradiol in healthy subjects.
- **Lorazepam, oxycodone and alcohol:** Multiple dose administration of pregabalin had no effect on the rate and extent of lorazepam, oxycodone, and alcohol. Likewise, single dose administration of lorazepam, oxycodone, and alcohol had no clinically significant effect on the steady state pharmacokinetics of pregabalin.
  Multiple oral doses of pregabalin concomitantly used with oxycodone, lorazepam, or ethanol did not result in clinically important effects on respiration. Pregabalin may potentiate the effects of alcohol and lorazepam. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone.
  In postmarketing experience, there are reports of respiratory failure and coma in patients taking pregabalin alone or in combination with other CNS depressants.
- **Antidiabetic agents:** A pharmacokinetic analysis showed no clinically significant effect on pregabalin clearance with the concomitant use of diurectics, oral hypoglycemic (e.g. glyburide, metformin), and insulin. Higher frequencies of weight gain and peripheral edema were reported in patients taking both pregabalin and a thiazolidinedione antidiabetic agent compared to patients taking either drug alone. As the thiazolidinedione class of antidiabetic drugs or pregabalin can cause weight gain and/or fluid retention alone or together, possibly exacerbating or leading to heart failure, caution should be exercised when co-administering pregabalin and these drugs.
- **Furosemide:** Furosemide does not appear to affect the pharmacokinetics of pregabalin.

STATEMENT ON USAGE FOR HIGH RISK GROUPS

PREGNANCY AND LACTATION

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.

Women of childbearing potential : As the potential risk for humans is unknown, effective contraception must be used in women of child bearing potential.

Labor and Delivery

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

Lactation

Pregabalin is excreted in the milk of breastfeeding women. As the safety of pregabalin in infants is not known, breastfeeding is not recommended in women taking pregabalin. A decision should be made whether to discontinue breastfeeding or to discontinue pregabalin therapy, taking into consideration the benefit of breastfeeding for the child and the benefit of therapy for the mother. Patients should be advised to notify their physician if they are breastfeeding.

Fertility

There are no clinical data on the effects of pregabalin on female fertility.

Pregabalin did not exhibit detrimental effects on the reproductive function of healthy male subjects, as measured by semen analysis, in a double-blind, placebo-controlled study to assess the effect of pregabalin on sperm motility.

RENAL IMPAIRMENT

There have been reports of patients, with or without previous history, experiencing renal failure while receiving pregabalin alone or in combination with other drugs. Discontinuation of pregabalin should be considered as it has shown reversibility of this event in some cases. Because pregabalin is eliminated primarily be renal excretion, the dose of pregabalin should be adjusted as noted for elderly patients or those with renal impairment. In patients with a medical history of significant renal insufficiency, daily dosages should be reduced accordingly.

CHILDREN

The safety and efficacy of pregabalin in pediatric patients have not been established.

ELDERLY

Pregabalin treatment has been associated with dizziness and somnolence, which may increase the occurrence of accidental injury (falls) in the elderly population.

UNDESIRABLE EFFECTS

Infections and infestations: Abscess, balanitis, cellulitis, epididymitis, flu syndrome, gangrene peripheral, halitosis, herpes simplex, herpes zoster, infection (bacterial, fungal, viral), moniliasis (oral, vaginal), moniliasis cutaneous, orchitis, salpingitis

Neoplasms benign, malignant and unspecified (incl cysts and polyps): Adenoma, carcinoma (bladder, breast, endometrial, thyroid, lung, prostatic, skin), chronic leukemia, macrocytic anemia, musculoskeletal congenital anomaly, neoplasia (CNS, laryngeal, prostate, thyroid, urogenital), neoplasm (bladder, bone, breast, cervix, thyroid), granuloma, ovarian cancer, sarcoma, skin benign neoplasia, skin melanoma

Blood and Lymphatic System Disorders: Anemia (hypochromic, macrocytic, megaloblastic), coagulation disorder, cyanosis, ecchymosis, eosinophilia, erythrocytes abnormal, hypochromic anemia, iron deficiency anemia, leukemoid reaction, leukocytosis, leukopenia, lymphadenopathy, lymphangitis, lymphedema, lymphocytosis, lymphoma like reaction, myelofibrosis, neutropenia, pancytopenia, petechiae, polycythemia, prothrombin decreased, purpura, rupture of spleen, splenomegaly, thrombocythemia, thrombocytopenia, thrombocytopenic purpura

Immune System Disorders: Allergic reaction, anaphylactoid reaction, angioedema, hypersensitivity, immune system disorder, retroperitoneal fibrosis, sarcoidosis, sepsis, Stevens-Johnson syndrome

Endocrine Disorders: Adrenal insufficiency, diabetes mellitus, goiter, hyperthyroidism, hypothyroidism, parathyroid disorder, prolactin increased, thyroid disorder, thyroiditis, virilism

Metabolism and Nutrition Disorders: Acidosis, alcohol intolerance, anorexia, appetite increased, avitaminosis, bilirubinemia, calcium disorder, dehydration, enzymatic abnormality, fluid retention, glucose tolerance decreased, gout, hypercholesterolemia, hyperglycemia, hyperlipemia, hyperuricemia, hypochloremia, hypoglycemia, hypoglycemic reaction, hypoproteinemia, ketosis, lactic acidosis, obesity, thirst, urate crystalluria, uremia

Psychiatric Disorders: Addiction, agitation, aggression, apathy, aphasia, anorgasmia, anxiety, confusional state, delirium, delusion, depersonalization, depression, disinhibition, disorientation, drug dependence, euphoric mood, hallucination, hostility, insomnia, irritability, manic reaction, mood swings, nervousness, panic attack, paralysis, paranoid reaction, personality disorder, psychosis, psychotic depression, restlessness, schizophrenic reaction, sleep disorder, suicide attempt, word finding difficulty

Nervous System Disorders: Abnormal dreams, ageusia, amnesia, ataxia, balance disorder, brain edema, burning sensation, CNS (depression, stimulation), cerebellar syndrome, cerebral infarct, cognitive disorder, cogwheel rigidity, coordination abnormal, coma, convulsion, dementia, disturbance in attention, dizziness, dizziness postural, dysautonomia, dysgraphia, dyskinesia, dystonia, encephalopathy, extrapyramidal syndrome, facial paralysis, foot drop, gait abnormal, Guillain-Barre syndrome, headache, hemiplegia, hypalgesia, hyperalgesia, hyperesthesia, hyperkinesia, hypoesthesia, hypokinesia, hyporeflexia, intracranial hypertension, incoordination, lethargy, loss of consciousness, intracranial aneurysm, memory impairment, meningitis, mental impairment, migraine, multiple sclerosis, myelitis, myoclonus, neuralgia, neuropathy, paresthesia, paresthesia circumoral, peripheral neuritis, psychomotor hyperactivity, reflexes decreased, sedation, somnolence, speech disorder, stupor, subarachnoid hemorrhage, tremor, tremor intention, thinking abnormal, torticollis, tremor, twitching, vertigo, vestibular disorder, withdrawal syndrome

Eye Disorders: Abnormal vision, abnormality of accommodation, anisocoria, asthenopia, blepharitis, blindness, blurred vision, cataract specified, color blindness, conjunctivitis, corneal lesion, corneal ulcer, corneal opacity, diplopia, dry eyes, exophthalmos, extraocular palsy, eye disorder, eye hemorrhage, eye irritation, eye pain, eye swelling, , iritis, keratitis, keratoconjunctivitis, lacrimation disorder, lacrimation increased, ophthalmoplegia, papilledema, mydriasis, night blindness, nystagmus, optic atrophy, oscillopsia, parosmia, peripheral vision loss, photophobia, photopsia, ptosis, refraction disorder, retinal artery occlusion, retinal degeneration, retinal depigmentation, retinal detachment, retinal disorder, retinal edema, retinal hemorrhage, retinal vein thrombosis, scleritis, strabismus, uveitis, visual acuity reduced, visual brightness, visual depth perception altered, visual disturbance, visual field defect, vision loss

Ear and Labyrinth Disorders: Ear pain, hyperaccusis, otitis externa, otitis media, tinnitus

Cardiac Disorders: Angina pectoris, arrhythmia (atrial), aortic stenosis, atrial fibrillation, atrial flutter, atrioventricular block (first degree, second degree), bradycardia, bradycardia sinus, bundle branch block, cardiomegaly, cardiomyopathy, carotid thrombosis, cerebral ischemia, congestive heart failure, coronary artery disorder, electrocardiogram abnormal, endocarditis, extrasystoles, extrasystole supraventricular, heart arrest, heart block, myocardial infarction, myocardial ischemia, occlusion (coronary, carotid), palpitation, QT interval prolonged/shortened, ST depressed/elevated, sinus arrhythmia, syncope, T inverted, tachycardia (nodal, sinus, supraventricular, ventricular), vascular headache, vasculitis, ventricular arrhythmia, ventricular extrasystole, ventricular fibrillation

Vascular Disorders: Arterial anomaly, arteriosclerosis, cerebral hemorrhage, cerebrovascular accident, embolus lower extremity, flushing, hemorrhage, hot flushes, hypertension, hypotension, hypertension postural, peripheral coldness, peripheral vascular disorder, pallor, petechiae, shock, phlebitis, thrombophlebitis deep, thrombosis, vascular anomaly, vascular disorder, vascular disorder retinal, vasodilatation

Respiratory, Thoracic and Mediastinal Disorders: Apnea, asthma, atelectasis, bronchiolitis, bronchitis, bronchiectasis, cough, dyspnea, emphysema, epistaxis, hiccup, hyperventilation, laryngismus, laryngitis, lung edema, lung disorder, lung edema, lung fibrosis, lung function decreased, hemoptysis, hiccup, hypoxia, hyposmia, hyperventilation, nasal dryness, nasal congestion, nasal septum disorder, nasopharyngitis, pharyngitis, pharyngolaryngeal pain, pleural disorder, pleural effusion, pneumonia, pneumonia aspiration, pneumothorax, pulmonary embolus, pulmonary hypertension, respiratory disorder, rhinitis, sinusitis, snoring, sputum increased, throat tightness, varicose vein, voice alteration, yawn

Gastrointestinal Disorders: Abdomen enlarged, abdominal distention, abdominal pain, aphthous stomatitis, ascites, bloody diarrhea, cardiospasm, cheilitis, cholelithiasis, cholecystitis, colitis, constipation, diarrhea, dry mouth, dysphagia, enteritis, enterocolitis, eructation, esophageal ulcer, esophagitis, fecal impaction, flatulence, gastritis, gastritis hemorrhagic, gastroenteritis, gastroesophageal reflux disease, gastrointestinal hemorrhage, gingivitis, glossitis, gum hyperplasia, hematemesis, hepatoma, hypoesthesia oral, intestinal obstruction, intestinal perforation, intestinal stenosis, leukoplakia of the mouth, melena, mouth ulceration, nausea, pancreas disorder, pancreatitis, pancreatitis necrotizing, paralytic ileus, periodontal abscess, periodontitis, pseudomembranous colitis, rectal disorder, rectal hemorrhage, salivary hypersecretion, salivary gland enlargement, sialadenitis, stomach atony, stomach ulcer, stomach ulcer hemorrhage, stools abnormal, stomatitis, swollen tongue, taste loss, taste perversion, tenesmus, tongue discoloration, tongue disorder, tongue edema, tooth caries, tooth disorder, ulcer (duodenal, intestinal, peptic), ulcerative colitis, vomiting

Hepatobiliary Disorders: Ascites, biliary pain, hepatitis, hepatomegaly, jaundice, jaundice cholestatic, liver fatty deposit, liver tenderness

Skin and subcutaneous Tissue Disorders: Acne, alopecia, angioedema, cold sweat, decubitus ulcer, dry skin, eczema, dermatitis (exfoliative, fungal, lichenoid), face swelling, furunculosis, hair disorder, Henoch-Schonlein purpura, hirsutism, ichthyosis, melanosis, miliria, nail disorder, photosensitivity reaction, rash (maculopapular, petechial, papular, purpuric, pustural, vesiculobullous), pruritus, psoriasis, seborrhea, skin atrophy, skin discoloration, skin disorder, skin hypertrophy, skin necrosis, skin nodule, skin ulcer, subcutaneous nodule, sweating, sweating decreased, urticaria

Musculoskeletal and Connective Tissue Disorders: Arthralgia, arthritis, arthrosis, bone disorder, bone pain, bursitis, cervical spasm, chondrodystrophy, dysarthria, generalized spasm, hypertonia, hypotonia, joint disorder, joint swelling, leg cramps, lupus erythematosus syndrome, muscle atrophy, muscle cramp, muscle spasms, muscle twitching, muscle stiffness, muscular weakness, myalgia, myasthenia, myopathy, myositis, neck rigidity, osteomyelitis, osteoporosis, pathological fracture, pyogenic arthritis, rhabdomyolysis, rheumatoid arthritis, tendinous contracture, tendon disorder, tendon rupture, tenosynovitis, trismus

Renal and Urinary Disorders: Acute kidney failure, albuminuria, balanitis, bladder calculus, calculus urinary, calculus, creatinine clearance decreased, cystitis, dyspareunia, dysuria, epididymitis, glomerulitis, glycosuria, hematuria, hydronephrosis, kidney calculus, kidney failure, kidney function abnormal, kidney pain, leukorrhea, mastitis, nephritis, nephrosis, nocturia, oliguria, polycystic kidney, polyuria, prostatic disorder, prostatic specific antigen increase, pyelonephritis, pyuria, renal failure, urethral pain, urethritis, urination impaired, urine abnormality, urinary frequency, urinary incontinence, urinary retention, urinary tract disorder, urinary urgency, urogenital disorder, urolithiasis, uterine disorder, uterine hemorrhage

Pregnancy, puerperium and perinatal conditions: Unintended pregnancy

Reproductive System and Breast Disorders: Abnormal ejaculation, amenorrhea, breast abscess, breast discharge, breast enlargement, breast pain, cervicitis, cervix disorder, dysmenorrhea, ejaculation delayed, endometrial disorder, erectile dysfunction, female lactation, fibrocystic breast, gynecomastia, hypomenorrhea, impotence, libido decreased/increased, menopause, menorrhagia, menstrual disorder, metrorrhagia, ovarian disorder, papanicolau smear suspicious, penis disorder, sexual dysfunction, uterine fibroids enlarged, vaginal hemorrhage, vaginitis, vulvovaginal disorder

General Disorders and Administration Site Conditions: Asthenia, body odor, chills, death, death sudden, edema (generalized, face, peripheral), fatigue, feeling abnormal, feeling drunk, fever, hangover effect, healing abnormal, hernia, hypothermia, joint swelling, malaise, mucous membrane disorder, pain (pelvic, neck, back, chest, limb), pain in extremities, reaction unevaluable, tolerance decreased, unexpected benefit

Investigations: Alanine aminotransferase increased, alkaline phosphatase increased, amylase increased, aspartate aminotransferase increased, blood calcium decreased/increased, blood creatine phosphokinase increased, blood creatinine increased, blood magnesium decreased, blood phosphate decreased, blood potassium decreased/increased, blood sodium increased, blood urea nitrogen increased, drug effect increased, drug level increased/decreased, gamma globulins increased, gamma glutamyl transpeptidase increased, gonadotropic follicle stimulating hormone increased, hormone level altered, medication error, non-protein nitrogen increased, platelet count decreased, sedimentation rate increased, weight increased/decreased, white blood cell count decreased

Injury, poisoning and procedural complications: Digitalis intoxication, fall, injury (accidental, intentional), medication error, overdose (accidental, intentional)

OVERDOSE AND TREATMENT

In overdoses up to 15 g, no unexpected adverse effects were reported. In postmarketing experience, fatal outcomes in cases in which pregabalin has been taken in combination with other drugs have been reported with a pregabalin overdose as low as 800 mg per day. In none of these cases has pregabalin been established as the cause of death or in pregabalin monotherapy.

The most commonly reported adverse events observed when pregabalin was taken in overdose (dose range: 800 mg/day to 11,500 mg as a single dose) include affective disorder, somnolence, confusional state, depression, agitation, and restlessness.

There is no specific antidote for pregabalin. Treatment of pregabalin overdose should be symptomatic and supportive including monitoring of vital signs and observation of the clinical status of the patient. Consider administration of activated charcoal in the event of a potentially toxic ingestion. Activated charcoal is most effective when administered within one hour of ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected.

Hemodialysis may be useful in patients with severe toxicity or those with significant renal impairment. Standard hemodialysis procedures result in significant clearance of pregabalin (approximately 50% in four hours). Emesis is not recommended because of the potential for CNS depression and seizures.

ADVERSE DRUG REACTION REPORTING STATEMENT

For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph **AND** Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

STORAGE CONDITIONS

Store at temperatures not exceeding 30˚C. Protect from light.

CAUTION

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

AVAILABILITY

Pregabalin 50 mg Capsule in ALU-PVC blister pack of 10's, box of 30 Capsules* - DR-XY42185
Pregabalin 75 mg Capsule in ALU-PVC blister pack of 10's, box of 30 Capsules - DR-XY41215
Pregabalin 150 mg Capsule in ALU-PVC blister pack of 10's, box of 30 Capsules - DR-XY41216

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