Xilica® (PREGABALIN)

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COMPOSITION
XILICA 25 mg Capsule
Each capsule contains: Pregabalin……25 mg
(As per innovator's specs.)

DESCRIPTION
XILICA capsules contain Pregabalin a CNS-active drug with anti-epileptic, anticonvulsant, and anti-nociceptive (pain inhibitory) effects. Pregabalin is chemically designated as (S)-3-(aminomethyl)-5-methylhexanoic acid. The molecular formula is $C_8H_{17}NO_2$

CLINICAL PHARMACOLOGY

Mechanism of Action
Pregabalin 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, it is suggested that binding to the alpha2-delta subunit may be involved in pregabalin's anti-nociceptive and antiseizure effects. 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 have acute effects on GABA concentration, 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

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 Tmax 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 is a substrate for system L transporter which is responsible for the transport of large amino acids across the blood brain barrier. 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.
Metabolism
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, accounts for 0.9% of the dose.
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 hemodialysis is necessary

INDICATIONS
XILICA (Pregabalin) is indicated for
• Management of neuropathic pain associated with diabetic peripheral neuropathy
• Management of post herpetic neuralgia
• Adjunctive therapy for the treatment of partial-onset seizures in patients 1 month of age and older
• Management of fibromyalgia
• Management of neuropathic pain associated with spinal cord injury.

DOSAGE AND ADMINISTRATION
Starting dose for all indications is 150 mg/day given as 2 or 3 divided doses.

Neuropathic Pain Associated with Diabetic Peripheral Neuropathy in Adults
The maximum recommended dose of XILICA 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.

Postherpetic Neuralgia in Adults
The recommended dose of XILICA 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.

Adjunctive Therapy for Partial-Onset Seizures in Patients 1 Month of Age and Older

Age and Body Weight	Recommended Initial Dosage	Recommended Maximum Dosage	Frequency of Administration
Adults (17 years and older)	150 mg/day	600 mg/day	2 or 3 divided doses
Pediatric patients weighing 30 kg or more	2.5 mg/kg/day	10 mg/kg/day (not to exceed 600 mg/day)	2 or 3 divided doses
Pediatric patients weighing less than 30 kg	3.5 mg/kg/day	14 mg/kg/day	1 month to less than 4 years of age: 3 divided doses 4 years of age and older: 2 or 3 divided doses

Management of Fibromyalgia in Adults
The recommended dose of XILICA 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).

Neuropathic Pain Associated with Spinal Cord Injury in Adults
The recommended dose range of XILICA 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 XILICA may be treated with up to 300 mg two times a day.

NOTE: When discontinuing Pregabalin, taper gradually over a minimum of 1 week.

Dosage adjustment and dosing consideration in special populations

Elderly (over 65 years of age)
Elderly patients may require a dose reduction of pregabalin due to a decreased renal function (see patients with renal impairment).
Patients with renal impairment
Pregabalin clearance is directly proportional to creatinine clearance, dose reduction in patients with compromised renal function must be individualized according to creatinine clearance (CrCl), as indicated in table below.
Pregabalin is removed effectively from plasma by hemodialysis (50% of drug in 4 hours). 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 following every 4-hour hemodialysis session

Pregabalin dose adjustment based on renal function

Creatinine clearance (CL_{cr})(ml/min)	Pregabalin daily dose *		Dose regimen
	Starting dose (mg/day)	Maximum dose (mg/day)	
≥ 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+

* Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose
\+ Supplementary dose is a single additional dose

Patients with hepatic impairment
No dose adjustment is required for patients with hepatic impairment.

Administration Requirements:
XILICA may be taken with or without food.

CONTRAINDICATIONS
XILICA is contraindicated in patients with known hypersensitivity to pregabalin. Angioedema and hypersensitivity reactions have occurred in patients receiving pregabalin therapy.

WARNINGS AND PRECAUTIONS

Weight gain and Diabetic patients
Pregabalin treatment may cause weight gain. Associated weight gain is related to dose and duration of exposure. Some diabetic patients who gain weight on pregabalin treatment may need to adjust their hypoglycemic medications.

Hypersensitivity reactions
There have been reports in the post marketing 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.

Nervous system effects
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 these potential effects of the drug.

Vision-related effects
Blurred vision has been reported with pregabalin compared to patients treated with placebo in clinical studies which resolved in a majority of cases with continued dosing. The incidence of visual acuity reduction and visual field changes in studies was greater in pregabalin-treated patients than in placebo-group; however 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.

Drug discontinuation and withdrawal symptoms
After discontinuation of short-term and long-term treatment with pregabalin, withdrawal symptoms such as insomnia, headache, nausea, anxiety, diarrhea, flu syndrome, nervousness, depression, pain, convulsion, hyperhidrosis and dizziness have been reported in some patients, suggestive of physical dependence. Convulsions, including status epileptics and grand mal convulsions, may occur during pregabalin use or shortly after discontinuing pregabalin. Patients should be informed prior to treatment.
The incidence and severity of withdrawal symptoms may be dose-related after long-term treatment. Pregabalin should be tapered gradually over a minimum of 1 week rather than discontinuing the drug abruptly.

Congestive heart failure
There have been postmarketing 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.

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 on pregabalin should be monitored for signs of suicidal ideation and behaviors and appropriate treatment should be considered. Patients and caregivers should be advised to seek medical advice should signs of suicidal ideation or behavior

emerge.

Reduced lower gastrointestinal tract function

There have been 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 are used in combination, measures to prevent constipation should be considered (especially in female patients and elderly).

Misuse, abuse potential or dependence

Cases of misuse, abuse and dependence 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 misuse, abuse or dependence (development of tolerance, dose escalation, drug-seeking behavior have been reported).

Encephalopathy

Cases of encephalopathy have been reported, mostly in patients with underlying conditions that may precipitate encephalopathy.

Peripheral Edema

Pregabalin treatment may cause peripheral edema. Higher frequency of peripheral edema has been reported in patients taking pregabalin with a thiazolidinedione antidiabetic drug. Thiazolidinedione class of drugs can cause weight gain and/or fluid retention, possibly exacerbating or leading to heart failure, therefore, caution should be exercised when co-administering Pregabalin with these agents.

In addition, caution is advised when using pregabalin in patients with congestive heart failure with New York Heart Association (NYHA) Class III or IV cardiac status.

Angioedema

There have been post-marketing reports of angioedema in patients during initial and chronic treatment with Pregabalin. Symptoms may include swelling of the face, mouth (tongue, lips, and gums), and neck (throat and larynx). There have been some reports of life-threatening angioedema with respiratory compromise. In such situations pregabalin should be discontinued immediately. Caution is needed in 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.

Creatine kinase elevations

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

Decreased platelet count

Treatment with pregabalin may be associated with decreased platelet count. However, bleeding related adverse reactions are unlikely.

PR interval prolongation

Pregabalin treatment may be associated with PR interval prolongation. However, there is no risk of association with second or third degree AV block adverse reactions. Higher risk of PR prolongation in patients with baseline PR prolongation or in patients taking other PR prolonging medications has not been reported or identified based on the available data.

Effects on ability to drive and use machines

Pregabalin may cause dizziness and somnolence and therefore may influence 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 drug affects their ability to perform these activities.

ADVERSE REACTIONS

The most commonly reported adverse reactions are dizziness and somnolence. Adverse reactions are usually mild to moderate in intensity. Following is the account of adverse reactions reported with pregabalin:

Infections and infestations
Common: Nasopharyngitis
Blood and lymphatic system disorders
Uncommon: Neutropenia
Immune system disorders
Uncommon: Hypersensitivity
Rare: Angioedema, allergic reaction
Metabolism and nutrition disorders
Common: Appetite increased
Uncommon: Anorexia, hypoglycemia
Psychiatric disorders
Common: Euphoric mood, confusion, irritability, disorientation, insomnia, libido decreased
Uncommon: Hallucination, panic attack, restlessness, agitation, depression, depressed mood, elevated mood, aggression, mood swings, depersonalization, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy
Rare: Disinhibition
Nervous system disorders
Very Common: Dizziness, somnolence, headache
Common: Ataxia, coordination abnormal, tremor, dysarthria, amnesia, memory impairment, disturbance in attention, paraesthesia, hypoaesthesia, sedation, balance disorder, lethargy
Uncommon: Syncope, stupor, myoclonus, loss of consciousness, psychomotor hyperactivity, dyskinesia, dizziness postural, intention tremor, nystagmus, cognitive disorder, mental impairment, speech disorder, hyporeflexia, hyperaesthesia, burning sensation, ageusia, malaise
Rare: Convulsions, parosmia, hypokinesia, dysgraphia
Eye disorders
Common: Vision blurred, diplopia
Uncommon: Peripheral vision loss, visual disturbance, eye swelling, visual field defect, visual acuity reduced, eye pain, asthenopia, photopsia, dry eye, lacrimation increased, eye irritation
Rare: Vision loss, keratitis, oscillopsia, altered visual depth perception, mydriasis, strabismus, visual brightness
Ear and labyrinth disorders
Common: Vertigo
Uncommon: Hyperacusis
Cardiac disorders
Uncommon: Tachycardia, atrioventricular block first degree, sinus bradycardia, congestive heart failure
Rare: QT prolongation, sinus tachycardia, sinus arrhythmia
Vascular disorders
Uncommon: Hypotension, hypertension, hot flushes, flushing, peripheral coldness
Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness
Rare: Pulmonary oedema, throat tightness
Gastrointestinal disorders
Common: Vomiting, nausea, constipation, diarrhea, flatulence, abdominal distension, dry mouth
Uncommon: Gastro esophageal reflux disease, salivary hyper secretion, hypoesthesia oral
Rare: Ascites, pancreatitis, swollen tongue, dysphagia
Skin and subcutaneous tissue disorders
Uncommon: Rash papular, urticaria, hyperhidrosis, pruritus
Rare: Stevens Johnson syndrome, cold sweat
Musculoskeletal and connective tissue disorders
Common: Muscle cramp, arthralgia, back pain, pain in limb, cervical spasm
Uncommon: Joint swelling, myalgia, muscle twitching, neck pain, muscle stiffness
Rare: Rhabdomyolysis
Renal and urinary disorders
Uncommon: Urinary incontinence, dysuria
Rare: Renal failure, oliguria, urinary retention
Reproductive system and breast disorders
Common: Erectile dysfunction
Uncommon: Sexual dysfunction, ejaculation delayed, dysmenorrhea, breast pain
Rare: Amenorrhea, breast discharge, breast enlargement, gynaecomastia
General disorders and administration site conditions
Common: Oedema peripheral, oedema, gait abnormal, fall, feeling drunk, feeling abnormal, fatigue
Uncommon: Generalized oedema, face oedema, chest tightness, pain, pyrexia, thirst, chills, asthenia
Investigations
Common: Weight increased
Uncommon: Blood creatine phosphokinase increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood glucose increased, platelet count decreased, blood creatinine increased, blood potassium decreased, weight decreased
Rare: White blood cell count decreased

DRUG INTERACTIONS

As 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.

Central nervous system influencing drugs

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 post marketing experience, there have been reports of respiratory failure and coma in patients taking pregabalin and other central nervous system (CNS) depressants. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone.

Thiazolidinediones

Pregabalin used concomitantly with thiazolidinediones may have additive effects on weight gain and peripheral edema. This may exacerbate or lead to heart failure.

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.

USE IN SPECIAL POPULATIONS

Pregnancy

There are no adequate data from the use of pregabalin in pregnant women. Studies in animals have shown reproductive developmental toxicity such as skeletal malformations, retarded ossification, and decreased fetal body weight. 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).

Nursing mothers

Pregabalin is excreted into human milk. The effect of pregabalin on newborns/infants is unknown. A decision must be made whether to discontinue breast-feeding or to discontinue pregabalin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Pediatrics

Neuropathic Pain Associated with Diabetic Peripheral Neuropathy, Postherpetic Neuralgia , and Neuropathic Pain Associated with Spinal Cord Injury
Safety and effectiveness in pediatric patients have not been established.

Fibromyalgia
Safety and effectiveness in pediatric patients have not been established.

Adjunctive Therapy for Partial-Onset Seizures
Safety and effectiveness in pediatric patients below the age of 1 month have not been established.

Elderly

Dose adjustment is required in elderly patients who have impaired renal function (see DOSAGE & ADMINISTRATION)

Renal impairment

Dose adjustment is required in renal impairment patients (see DOSAGE & ADMINISTRATION)

Hepatic impairment

No dose adjustment is required for patients with hepatic impairment patients

OVER DOSAGE

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. In rare occasions, cases of coma have been reported.

There is no specific antidote for overdose with Pregabalin. If indicated, elimination of unabsorbed drug may be attempted by emesis or gastric lavage; observe usual precautions to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient. 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).

PRESENTATION

XILICA 25 mg : Pack of 14 capsules

INSTRUCTIONS

Use as advised by the physician.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Protect from light, heat and moisture.
Store below 30°C.
For suspected adverse drug reaction, email us at reports@pharmevo.biz

For more information on our products
call PharmAssist helpline 0800-82222
Monday to Friday 9:00 am to 6:00 pm
or email us at : pharmassist@pharmevo.biz

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