1. NAME OF THE MEDICINAL PRODUCT

PREGALIX 75mg Capsules
PREGALIX 150mg Capsules

2. NAME AND STRENGTH OF ACTIVE SUBSTANCES

Pregabalin 75mg
Pregabalin 150mg

3. PRODUCT DESCRIPTION

PREGALIX 75mg Capsules
Opaque white/ Orange Opaque size "4" Hard gelatin capsules radially imprinted with 'A' on cap and '142' on body with black ink filled with white to off white powder.

PREGALIX 150mg Capsules
Opaque white/ opaque white size "2" Hard gelatin capsules radially imprinted with 'A' on cap and '144' on body with black ink filled with white to off white powder.

4. DOSAGE FORM

Hard Gelatin Capsule

5. PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Anti-epileptics, other anti-epileptics

ATC code: N03AX16 The active substance, pregabalin, is a gamma-aminobutyric acid analogue [(S) -3- (aminomethyl) -5-methylhexanoic acid].

Mechanism of action

Pregabalin binds to an auxiliary subunit (α2-δ protein) of voltage-gated calcium channels in the central nervous system,

Clinical efficacy and safety

Neuropathic pain

Efficacy has been shown in diabetic neuropathy, post herpetic neuralgia and spinal cord injury. Safety and efficacy profiles for BID and TID dosing regimens are similar. For both pheripheral and central neuropathic pain, a reduction in pain is seen by Week 1 and it maintained throughout the treatment period.

Epilepsy

Adjunctive Treatment

The safety and efficacy profiles for BID and TID dosing regimens are similar. A reduction in seizure frequency is observed by Week 1.

Paediatric population

The efficacy and safety of pregabalin as adjunctive treatment for epilepsy in paediatric patients below the age of 12 and in adolescents has not been established.

Monotherapy (newly diagnosed patients)

Pregabalin and lamotrigine are similarly safe and well tolerated.

Generalized anxiety disorder

Relief of the symptoms of GAD as reflected by the Hamilton Anxiety Rating Scale (HAM-A) is observed by Week 1. Patients treated with pregabalin reported blurred vision which resolved in a majority of cases with continued dosing.

6. PHARMACOKINETIC PROPERTIES

Pregabalin steady-state pharmacokinetics are similar in healthy volunteers, patients with epilepsy receiving anti-epileptic drugs and patients with chronic pain.

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

Pregabalin has been shown to cross the blood brain barrier in mice, rats, and monkeys. 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.

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.

Gender

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

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.

Paediatric population

After oral administration of pregabalin in paediatric patients in the fasted state, in general, time to reach peak plasma concentration was similar across the entire age group and occurred 0.5 hours to 2 hours postdose.

Pregabalin terminal half-life averaged about 3 to 4 hours in paediatric patients up to 6 years of age, and 4 to 6 hours in those 7 years of age and older.

Population pharmacokinetic analysis showed that creatinine clearance was a significant covariate of pregabalin oral clearance, body weight was a significant covariate of pregabalin apparent oral volume of distribution, and these relationships were similar in paediatric and adult patients.

Elderly

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.

Breast-feeding mothers

Lactation had little to no influence on pregabalin pharmacokinetics. Pregabalin was excreted into breast milk with average steady-state concentrations approximately 76% of those in maternal plasma. The estimated infant dose from breast milk (assuming mean milk consumption of 150 ml/kg/day) of women receiving 300 mg/day or the maximum dose of 600 mg/day would be 0.31 or 0.62 mg/kg/day, respectively. These estimated doses are approximately 7% of the total daily maternal dose on a mg/kg basis.

7. INDICATIONS

Neuropathic pain
Pregabalin is indicated for the treatment of peripheral and central neuropathic pain in adults.

Epilepsy
Pregabalin is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.

Generalised anxiety disorder
Pregabalin is indicated for the treatment of Generalised Anxiety Disorder (GAD) in adults.

Fibromyalgia
Pregabalin is indicated for the management of Fibromyalgia.

8. RECOMMENDED DOSAGE

Posology

The dose range is 150 to 600 mg per day given in either two or three divided doses.

Pregabalin may be taken with or without food.

Neuropathic pain

Pregabalin treatment can be started at a dose of 150 mg per day. Based on individual patient response and tolerability, the dose may be increased to 300 mg per day after an interval of 3 to 7 days, and if needed, to a maximum dose of 600 mg per day after an additional 7-day interval.

Fibromyalgia

The usual dose range for most patients is 300 to 450mg per day given in two divided doses. Some

patients may derive additional benefit at 600mg per day. Dosing should begin at 75mg two times a day (150 mg/day) and may be increased to 150mg two times a day (300mg/day) within 1 week based on efficacy and tolerability. Patients who do not experience sufficient benefit with 300mg/day may be further increased to 225 mg two times a day (450mg/day). If needed, in some patients, based on individual response and tolerability, the dose may be increased to maximum dosage of 600mg/day after an additional week.

Epilepsy

Pregabalin treatment can be started with a dose of 150 mg per day. Based on individual patient response and tolerability, the dose may be increased to 300 mg per day after 1 week. The maximum dose of 600 mg per day may be achieved after an additional week.

Generalised anxiety disorder

The dose range is 150 to 600 mg per day given as two or three divided doses. The need for treatment should be reassessed regularly.

Pregabalin treatment can be started with a dose of 150mg per day. Based on individual patient response and tolerability, the dosage may be increased to 300mg per day after one week. Following an additional week the dosage may be increased to 450mg per day. The maximum dosage of 600mg per day may be achieved after an additional week.

Discontinuation of pregabalin

If pregabalin has to be discontinued, it is recommended this should be done gradually over a minimum of 1 week.

Patients with Renal impairment

Dosage reduction in patients with compromised renal function must be individualized accordingly to creatinine clearance (CLcr) as indicated in Table 1 determined using the following formula:

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

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).

Table 1. Pregabalin Dose Adjustment Based on Renal Function

Creatinine clearance (CLcr)	Total 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	QD
Supplementary dosage following haemodialysis (mg)			
	25	100	Single dose+

TID = Three divided doses BID = Two divided doses QD = single daily dose.

* Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose

+ Supplementary dose is a single additional dose

Use in patients with Hepatic impairment

No dose adjustment is required for patients with hepatic impairment.

Use in children and adolescents (12 to 17 years of age)

The safety and effectiveness of pregabalin in pediatric patients below the age of 12 years and adolescents have not been established. The use in children is not recommended.

Use in the elderly (over 65 years of age)

Elderly patients may require a dose reduction of pregabalin due to a decreased renal function.

9. METHOD OF ADMINISTRATION

Pregabalin may be taken with or without food. Pregabalin is for oral use only.

10. CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed below:

Capsule content: Pregelatinized Starch (Starch 1500 LM), Talc

Capsule shell (for 75 mg) : Gelatin, Water, Iron Oxide Red, Titanium Dioxide,

Capsule shell (for 150mg) : Gelatin, Water, Titanium Dioxide.

11. WARNING AND PRECAUTIONS

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 postmarketing 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 the 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.

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 anti-epileptic medicinal products, once seizure control with pregabalin in the add-on situation has been reached, in order to reach monotherapy on pregabalin. Potential for an increase in risk of suicidal thoughts or behaviors.

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, diarrhoea, 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 symptoms may be dose-related.

Congestive heart failure

There have been 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.

Treatment of central neuropathic pain due to spinal cord injury

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

Suicidal ideation and behavior

Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Reduced lower gastrointestinal tract function

There are 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).

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 behaviour have been reported).

Encephalopathy

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

12. INTERACTIONS WITH OTHER MEDICAMENTS

Since pregabalin is predominantly excreted unchanged in the urine, it is unlikely to produce or subject to, pharmacokinetic interactions.

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.

Central nervous system influencing medical products

Pregabalin may potentiate the effects of ethanol and lorazepam. There are reports of respiratory failure and coma in patients taking pregabalin and other central nervous system (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.

13. STATEMENT ON USAGE DURING PREGNANCY AND LACTATION

Women of childbearing potential / Contraception in males and females

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

Pregnancy

There are no adequate data from the use of pregabalin in pregnant women. 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 foetus).

Breast-feeding

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.

14. ADVARSE EFFECTS / UNDESIRABLE EFFECTS

Adverse reactions were usually mild to moderate in intensity. The most common adverse reactions resulting in discontinuation from pregabalin treatment groups were dizziness and somnolence.

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

In the treatment of central neuropathic pain due to spinal cord injury the incidence of adverse reactions in

general, CNS adverse reactions and especially somnolence was increased.Fse

Additional reactions reported from post-marketing experience are included in italics in the list below.

Table 2. Pregabalin Adverse Drug Reactions

System Organ Class	Adverse drug reactions
Infections and infestations	
Common	Nasopharyngitis
Blood and lymphatic system disorders	
Uncommon	Neutropaenia
Immune system disorders	
Uncommon	*Hypersensitivity*
Rare	*Angioedema, allergic reaction*
Metabolism and nutrition disorders	
Common	Appetite increased
Uncommon	Anorexia, hypoglycaemia
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, depersonalisation, 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	

System Organ Class	Adverse drug reactions
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	Dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness
Rare	*Pulmonary oedema*, throat tightness,
Gastrointestinal disorders	
Common	Vomiting, *nausea*, constipation, *diarrhoea*, flatulence, abdominal distension, dry mouth
Uncommon	Gastrooesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral
Rare	Ascites, pancreatitis, *swollen tongue*, dysphagia
Hepatobiliary disorders	
Uncommon	Elevated liver enzymes*
Rare	Jaundice
Very rare	Hepatic failure, hepatitis
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, dysmenorrhoea, breast pain
Rare	Amenorrhoea, breast discharge, breast enlargement, *gynaecomastia*

System Organ Class	Adverse drug reactions
General disorders and administration site conditions	
Common	Oedema peripheral, oedema, gait abnormal, fall, feeling drunk, feeling abnormal, fatigue
Uncommon	Generalised oedema, *face oedema*, chest tightness, pain, pyrexia, thirst, chills, asthenia
Investigations	
Common	Weight increased
Uncommon	Blood creatine phosphokinase increased, blood glucose increased, platelet count decreased, blood creatinine increased, blood potassium decreased, weight decreased
Rare	White blood cell count decreased

* Alanine aminotransferase increased (ALT) and aspartate aminotransferase increased (AST).

After discontinuation of short-term and long-term treatment with pregabalin withdrawal symptoms have been observed in some patients. The following reactions have been mentioned: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, convulsions, nervousness, depression, pain**,** hyperhidrosis and dizziness, suggestive of physical dependence. The patient should be informed about this at the start of the treatment.

Concerning discontinuation of long-term treatment of pregabalin, data suggest that the incidence and severity of withdrawal symptoms may be dose-related.

Paediatric population

The most common adverse events observed with pregabalin treatment were somnolence, pyrexia, upper respiratory tract infection, increased appetite, weight increased, and nasopharyngitis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

15. OVERDOSAGE AND TREATMENT

In the postmarketing experience, the most commonly reported adverse reactions observed when pregabalin was taken in overdose included somnolence, confusional state, agitation, and restlessness. Seizures were also reported.

In rare occasions, cases of coma have been reported.

Treatment of pregabalin overdose should include general supportive measures and may include haemodialysis if necessary.

16. EFFECTS ON ABILITY TO DRIVE AND USE MACHINE

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

17. STORAGE CONDITION

Store below 30◦C. Keep in a cool, dry place away from sunlight.

18. PACKAGING AVAILABLE

14 capsules per blister strip.
4 blister strips are packed into an outer carton.

19. NAME AND ADDRESS OF PRODUCT REGISTRATION HOLDER

Genpharma Sdn. Bhd.
Lot 5016, Jalan Teratai,
$5^{1/2}$, Mile off Jalan Meru,
41050 Klang, Selangor
Malaysia.

20. NAME AND ADDRESS OF MANUFACTURER

Alembic Pharmaceuticals Limited
Vill. Panelav, Post – Tajpura,
Tal - Halol, District, Panchmahal,
389350 Gujarat,
India.

21. DATE OF REVISION

01/September/2020