160X227

Natrapharm

PREGABALIN

NERVAGEST®

75 mg Capsule

Antiepileptic

Formulation:
Each capsule contains:
Pregabalin ..... 75 mg

Indication
1.Adjunctive therapy in adults with partial seizures with or without secondary generalization.
2.Treatment of Generalized Anxiety Disorder (GAD) in adults.

Dosage & Administration
Epilepsy
Adult : Pregabalin treatment can be started at a dose of 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 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.

Generalized Anxiety Disorder
Adult: The dose range is 150 to 600 mg per day given as two to three divided doses. The need for treatment should be reassessed regularly.
Pregabalin treatment can be started at a dose of 150mg per day. Based on individual patient response and tolerability, the dose may be increased to 450mg per day. The maximum dose of 600mg per day may be achieved after an additional 7 days.

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.

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 patient with compromised renal function must be individualized according to creatinine clearance(CLcr), as indicated in Table 1 determined using the following formula :

CLcr (mL/min) =
([140 – age(years)] × weight(kg)) / (72 × serum creatinine(mg/dL)) (× 0.85 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 hours haemodialysis treatment (see Table 1).

Table 1. Pregabalin dose adjustment based on renal function

Creatinine Clearance (CLcr) (mL/min)	Total pregabalin daily dose*a		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*b

TID = Three divided doses
BID = Two divided doses
*a : Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose
*b : Supplementary dose is a single additional dose

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

Pediatric population
The safety and efficacy in children below the age of 12 years and in adolescents (12~17 years of age) have not been established. No data are available.

Elderly (over 65 years of age)
Elderly patients may require a dose reduction of pregabalin due to a decreased renal function.

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

Contraindications
Hypersensitivity to the active substance or to any of the excipients.

Special warning
Suicidal ideation and Behaviour
1. Antiepileptic drugs (AEDs) 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.
2. Anyone considering prescribing 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.

Precautions for use
1. Diabetic Patients
In accordance with current clinical practice, some diabetic patients who gain weight on pregabalin treatment may need to adjust hypoglycaemic medicinal products.

2. 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.

3. 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.

4. Vision-related effects
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.

5. 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.

6. 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.

7. Renal failure
Cases of renal failure have been reported and in some cases discontinuation of pregabalin did show reversibility of this adverse reaction.

8. Congestive heart failure
There have been post-marketing reports of congestive heart failure in some patients receiving pregabalin. Pregabalin should be used with caution in these patients. Discontinuation of pregabalin may resolve the reaction.

Adverse effects
The pregabalin clinical programme involved over 12,000 patients who were exposed to pregabalin, of whom over 7,000 were in double-blind placebo controlled trials. The most commonly reported adverse reactions were dizziness and somnolence. Adverse reactions were usually mild to moderate in intensity. In all controlled studies, the discontinuation rate due to adverse reactions was 14% for patients receiving pregabalin and 5% for patients receiving placebo. The most common adverse reactions resulting in discontinuation from pregabalin treatment groups were dizziness and somnolence.

In the table below all adverse reactions, which occurred at an incidence greater than placebo and in more than one patient, are listed by class and frequency (very common (≥1/10); common (≥1/100 to< 1/10); uncommon (≥1/1,000 to<1/100); rare (≤ 1/1,000); very rare (≤1/10,000) not known (cannot be estimated from the available data).

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

System Organ Class	Adverse drug reactions
Infections and infestations	
Uncommon	Nasopharyngitis
Blood and lymphatic system disorders	
Rare	Neutropenia
Immune system disorders	
Frequency not known	Hypersensitivity, angioedema, allergic reaction
Metabolism and nutrition disorders	
Common	Appetite increased
Uncommon	Anorexia
Rare	Hypoglycaemia
Psychiatric disorders	
Common	Euphoric mood, confusion, irritability, libido decreased, disorientation, insomnia
Uncommon	Hallucination, panic attack, restlessness, agitation, depression, depressed mood, mood swings, depersonalization, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy
Rare	Disinhibition, elevated mood
Nervous system disorders	
Very Common	Dizziness, somnolence
Common	Ataxia, coordination abnormal, tremor, dysarthria, memory impairment, disturbance in attention, paraesthesia, sedation, balance disorder, lethargy, amnesia
Uncommon	Syncope, stupor, myoclonus, psychomotor hyperactivity, ageusia, dyskinesia, dizziness postural, intention tremor, nystagmus, cognitive disorder, speech disorder, hyporeflexia, hypoaesthesia, hyperaesthesia, burning sensation
Rare	Hypokinesia, parosmia, dysgraphia
Frequency not known	Loss of consciousness, mental impairment, headache
Eye disorders	
Common	Vision blurred, diplopia
Uncommon	Visual disturbance, eye swelling, visual field defect, visual acuity reduced, eye pain, asthenopia, lacrimation increased
Rare	Peripheral vision loss, oscillopsia, altered visual depth perception, photopsia, eye irritation, mydriasis, strabismus, visual brightness
Frequency not known	Keratitis
Ear and labyrinth disorders	
Common	Vertigo
Uncommon	Hyperacusis
Cardiac disorders	
Uncommon	Tachycardia, atrioventricular block first degree
Rare	Sinus tachycardia, sinus bradycardia, sinus arrhythmia
Frequency not known	Congestive heart failure
Vascular disorders	
Uncommon	Flushing, hot flushes, hypotension, hypertension, peripheral coldness
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, cough, nasal dryness
Rare	Epistaxis, throat tightness, nasal congestion, rhinitis, snoring
Frequency not known	Pulmonary oedema
Gastrointestinal disorders	
Common	Vomiting, dry mouth, constipation, flatulence, abdominal distension
Uncommon	Gastrooesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral
Rare	Ascites, pancreatitis, dysphagia
Frequency not known	Swollen tongue, diarrhea, nausea
Skin and subcutaneous tissue disorders	
Uncommon	Rash papular, hyperhidrosis
Rare	Urticaria, cold sweat
Frequency not known	Facial swelling, pruritus
Musculoskeletal and connective tissue disorders	
Uncommon	Muscle twitching, joint swelling, muscle cramp, myalgia, arthralgia, back pain, pain in limb, muscle stiffness
Rare	Rhabdomyolysis, cervical spasm, neck pain
Renal and urinary disorders	
Uncommon	Urinary incontinence, dysuria
Rare	Renal failure, oliguria
Frequency not known	Urinary retention
Reproductive system and breast disorders	
Common	Erectile dysfunction
Uncommon	Ejaculation delayed, sexual dysfunction
Rare	Amenorrhoea, breast discharge, breast pain, dysmenorrhoea, breast enlargement
Frequency not known	Gynaecomastia
General disorders and administration site conditions	
Common	Gait abnormal, feeling drunk, fatigue, peripheral edema, edema
Uncommon	Fall, chest tightness, asthenia, thirst, pain, chills, generalized edema
Rare	Pyrexia
Frequency not known	Malaise
Investigations	
Common	Weight increased
Uncommon	Blood creatine phosphokinase increased, alanine aminotransferase increased, aspartate aminotransferase increased, platelet count decreased
Rare	Blood glucose increased, blood potassium decreased, white blood cell count decreased, blood creatinine increased, weight decreased

Interaction with other drugs
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.

Use in Pregnancy & lactation
1. Pregnant Women
There are no adequate data from the use of pregabalin in pregnant women.
Studies in animals have shown reproductive toxicity. The potential risk for human 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).

2. Lactation
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.

Effects on ability to drive and operate 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 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 medicinal product affects their ability to perform these activities.

Overdose
In overdose up to 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.

Pharmacological Properties

1. Pharmacodynamic properties
Mechanism of action
Pregabalin binds to an auxiliary subunit (α_2-δ protein) of voltage-gated calcium channels in the central nervous system,

Clinical experience

Epilepsy
Adjunctive Treatment
Pregabalin has been studied in 3 controlled clinical trials of 12 week duration with either twice a day dosing (BID) or three times a day (TID) dosing. Overall, the safety and efficacy profiles for BID and TID dosing regimens were similar.

A reduction in seizure frequency was observed by Week 1.

Monotherapy (newly diagnosed patients)
Pregabalin has been studied in 1 controlled clinical trial of 56 week duration with twice a day dosing (BID). Pregabalin did not achieve non-inferiority to lamotrigine based on the 6-month seizure freedom endpoint. Pregabalin and lamotrigine were similarly safe and well tolerated.

Generalized Anxiety Disorder
Pregabalin has been studied in 6 controlled trials of 4-6 weeks duration, an elderly study of 8 week duration and a long-term relapse prevention study with a double blind relapse prevention phase of 6 months duration.
Relief of the symptoms of GAD as reflected by the Hamilton Anxiety Rating Scale (HAM-A) was observed by week 1.
In controlled clinical trials, a higher proportion of patients treated with pregabalin reported blurred vision than with patients treated with placebo which resolved in majority of cases with continued dosing. Ophthalmologic testing (including visual acuity testing, formal visual field testing and dilated funduscopic examination) was conducted in over 3600 patients within controlled clinical trials. In these patients, visual acuity was reduced in 6.5% of patients treated with pregabalin, and 4.6% of placebo-treated patients. Visual field changes were detected in 12.4% of pregabalin-treated patients and 11.7% of placebo-treated patients. Funduscopic changes were observed in 1.7% of pregabalin-treated and and 2.1% of placebo-treated patients.

2. 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 C_{max} 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.

3. Preclinical Safety Data
In conventional safety pharmacology studies in animals, pregabalin was well-tolerated at clinically relevant doses. In repeated dose toxicity studies in rats and monkeys CNS effects were observed, including hypoactivity, hyperactivity and ataxia. An increased incidence of retinal atrophy commonly observed in aged albino rats was seen after long term exposure to pregabalin at exposures ≥ 5 times the mean human exposure at the maximum recommended clinical dose. Pregabalin was not teratogenic in mice, rats or rabbits. Foetal toxicity in rats and rabbits occurred only at exposures sufficiently above human exposure. In prenatal/postnatal toxicity studies, pregabalin induced offspring developmental toxicity in rats at exposures >2 times the maximum recommended human exposure.
Adverse effects on fertility in male and female rats were only observed at exposures sufficiently in excess of therapeutic exposure. Adverse effects on male reproductive organs and sperm parameters were reversible and occurred only at exposures sufficiently in excess of therapeutic exposure or were associated with spontaneous degenerative processes in male reproductive organs in the rat. Therefore the effects were considered of little or no clinical relevance.
Pregabalin is not genotoxic based on results of a battery of *in vitro* and *in vivo* tests.
Two-year carcinogenicity studies with pregabalin were conducted in rats and mice. No tumours were observed in rats at exposures up to 24 times the mean human exposure at the maximum recommended clinical dose of 600 mg/day. In mice, no increased incidence of tumours was found at exposures similar to the mean human exposure, but an increased incidence of haemangiosarcoma was observed at higher exposures. The non-genotoxic mechanism of pregabalin-induced tumour formation in mice involves platelet changes and associated endothelial cell proliferation. These platelet changes were not present in rats or in humans based on short term and limited long term clinical data. There is no evidence to suggest an associated risk to humans.
In juvenile rats the types of toxicity do not differ qualitatively from those observed in adult rats. However, juvenile rats are more sensitive. At therapeutic exposures, there was evidence of CNS clinical signs of hyperactivity and bruxism and some changes in growth (transient body weight gain suppression). Effects on the oestrus cycle were observed at 5-fold the human therapeutic exposure. Reduced acoustic startle response was observed in juvenile rats 1-2 weeks after exposure at >2 times the human therapeutic exposure. Nine weeks after exposure, this effect was no longer observable.

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

Storage
Store at temperatures not exceeding 30℃.

Availability
Alu/Clear PVC blister pack of 10 capsules (30 capsules per box)

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph
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TO COMPLY WITH AO 2016-0008

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