For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

Neurogab 75 (Pregabalin Capsules 75mg)
Neurogab 150 (Pregabalin Capsules 150mg)

COMPOSITION
Each capsule contains:
Pregabalin USP…….75/150 mg

DESCRIPTION
For 75mg: Orange/White size '4' hard gelatin capsules imprinted with 'M3' on cap and '75mg' on body containing white coloured powder.
For 150 mg: White / white, size "2", hard gelatin capsules imprinted with "M5" on cap and " 150 mg " on body containing white coloured powder.

PHARMACODYNAMICS
Pharmacotherapeutic group: Antiepileptics, ATC code: N03A (proposed).
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 (α_2-δ protein) of voltage-gated calcium channels in the central nervous system.

Evidence from animal models with nerve damage has shown that pregabalin reduces calcium dependent release of pronociceptive neurotransmitters in the spinal cord possibly by disrupting calcium trafficking and/or reducing calcium currents. Evidence from other animal models of nerve damage suggest the antinociceptive activities of pregabalin may also be mediated through interactions with the descending noradrenergic and serotonergic pathways.

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 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 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 radiolabeled pregabalin, approximately 98% of the administered dose was recovered in the urine as unchanged pregabalin. The N-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0.9% of the dose.

Excretion
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 hemodialysis (following a 4-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 following hemodialysis 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.

Breast-feeding mothers
The pharmacokinetics of 150 mg pregabalin given every 12 hours (300 mg daily dose) was evaluated in 10 lactating women who were at least 12 weeks postpartum. 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 average daily infant dose of pregabalin from breast milk (assuming mean milk consumption of 150 mL/kg/day) was 0.31 mg/kg/day, which on a mg/kg basis would be approximately 7% of the maternal dose.

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.

RECOMMENDED DOSAGE
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 dosage 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 450 mg per day given in two divided doses. Some patients may derive additional benefit at 600 mg per day. Dosing should begin at 75 mg two times a day (150 mg/day) and 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). If needed, in some patients, based on individual response and tolerability, the dose may be increased to maximum dosage of 600 mg/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 dosage may be increased to 300 mg per day after 1 week. The maximum dosage 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 150 mg per day. Based on individual patient response and tolerability, the dosage may be increased to 300 mg per day after 1 week. Following an additional week the dosage may be increased to 450 mg per day. The maximum dosage of 600 mg 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 individualised according to creatinine clearance (CLcr) as indicated in below table determined using the following formula:

$$\text{CLcr (mL/min)} = \left[\frac{[140 - \text{age(years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}\right] (\times 0.85 \text{ for female patients})$$

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 haemodialysis treatment.

Table: Pregabalin Dosage Adjustment Based on Renal Function

	Total Pregabalin Daily Dose*		
Creatinine Clearance (CLcr) (mL/min)	Starting Dose (mg/day)	Maximum Dose (mg/day)	Dose Regimen
≥60	150	600	BID or TID
≥30 - <60	75	300	BID or TID
≥15 - <30	25 – 50	175	QD 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 dosage 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 has 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 decreased renal function.

MODE OF ADMINISTRATION: Oral Capsules

CONTRAINDICATIONS
Pregabalin is contraindicated in patients with known hypersensitivity to pregabalin or any of its components. Angioedema and hypersensitivity reactions have occurred in patients receiving pregabalin therapy.

WARNINGS & PRECAUTIONS
Angioedema
There have been post-marketing reports of angioedema in patients during initial and chronic treatment with pregabalin. Specific symptoms included swelling of the face, mouth (tongue, lips, and gums), and neck (throat and larynx). There were reports of life-threatening angioedema with respiratory compromise requiring emergency treatment. Discontinue pregabalin immediately in patients with these symptoms.
Exercise caution when prescribing pregabalin to patients who have had a previous episode of angioedema. In addition, patients who are taking other drugs associated with angioedema (e.g., angiotensin converting enzyme inhibitors [ACE-inhibitors]) may be at increased risk of developing angioedema.

Hypersensitivity
There have been post-marketing 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.

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.
Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.
The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.
The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed.
Below table shows absolute and relative risk by indication for all evaluated AEDs.

Table: Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.
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.

Respiratory Depression
There is evidence from case reports, human studies, and animal studies associating pregabalin with serious, life-threatening, or fatal respiratory depression when co-administered with central nervous system (CNS) depressants, including opioids, or in the setting of underlying respiratory impairment. When the decision is made to co-prescribe pregabalin with another CNS depressant, particularly an opioid, or to prescribe pregabalin to patients with underlying respiratory impairment, monitor patients for symptoms of respiratory depression and sedation, and consider initiating pregabalin at a low dose. The management of respiratory depression may include close observation, supportive measures, and reduction or withdrawal of CNS depressants (including pregabalin).
There is more limited evidence from case reports, animal studies, and human studies associating pregabalin with serious respiratory depression, without co-administered CNS depressants or without underlying respiratory impairment.

Dizziness and Somnolence
Pregabalin may cause dizziness and somnolence. Inform patients that pregabalin-related dizziness and somnolence may impair their ability to perform tasks such as driving or operating machinery and could increase the occurrence of accidental injury (fall) in the elderly population.
In the pregabalin controlled trials in adult patients, dizziness was experienced by 30% of pregabalin-treated patients compared to 8% of placebo-treated patients; somnolence was experienced by 23% of pregabalin-treated patients compared to 8% of placebo-treated patients. Dizziness and somnolence generally began shortly after the initiation of pregabalin therapy and occurred more frequently at higher doses. Dizziness and somnolence were the adverse reactions most frequently leading to withdrawal (4% each) from controlled studies. In pregabalin-treated patients reporting these adverse reactions in short-term, controlled studies, dizziness persisted until the last dose in 30% and somnolence persisted until the last dose in 42% of patients.

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 medication.
Pregabalin is not known to be active at receptor sites associated with drugs of abuse. Cases of misuse, abuse, and dependence have been reported in the post-marketing database. As with any CNS active drug, carefully evaluate patients for history of drug abuse and/or psychiatric disorders. Patients should be observed for signs of pregabalin misuse, abuse or dependence (e.g., development of tolerance, dose escalation, drug-seeking behavior).

Increased Risk of Adverse Reactions with Abrupt or Rapid Discontinuation
As with all antiepileptic drugs (AEDs), withdraw pregabalin gradually to minimize the potential of increased seizure frequency in patients with seizure disorders.
Following abrupt or rapid discontinuation of Pregabalin, some patients reported symptoms including insomnia, nausea, headache, anxiety, hyperhidrosis, and diarrhea.
If Pregabalin is discontinued, taper the drug gradually over a minimum of 1 week rather than discontinue the drug abruptly.

Peripheral Edema
Pregabalin treatment may cause peripheral edema. In short-term trials of patients without clinically significant heart or peripheral vascular disease, there was no apparent association between peripheral edema and cardiovascular complications such as hypertension or congestive heart failure. Peripheral edema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function.
In controlled clinical trials in adult patients, the incidence of peripheral edema was 6% in the pregabalin group compared with 2% in the placebo group. In controlled clinical trials, 0.5% of pregabalin patients and 0.2% placebo patients withdrew due to peripheral edema.
Higher frequencies of weight gain and peripheral edema were observed in patients taking both pregabalin and a thiazolidinedione antidiabetic agent compared to patients taking either drug alone. The majority of patients using thiazolidinedione antidiabetic agents in the overall safety database were participants in studies of pain associated with diabetic peripheral neuropathy. In this population, peripheral edema was reported in 3% (2/60) of patients who were using thiazolidinedione antidiabetic agents only, 8% (69/859) of patients who were treated with pregabalin only, and 19% (23/120) of patients who were on both pregabalin and thiazolidinedione antidiabetic agents. Similarly, weight gain was reported in 0% (0/60) of patients on thiazolidinediones only; 4% (35/859) of patients on pregabalin only; and 7.5% (9/120) of patients on both drugs.
As the thiazolidinedione class of antidiabetic drugs can cause weight gain and/or fluid retention, possibly exacerbating or leading to heart failure, exercise caution when co-administering pregabalin and these agents.
Although there has been no causal relationship identified between exposure to pregabalin and congestive heart failure, there has been post-marketing reports of congestive heart failure in some patients receiving pregabalin. In short-term trials of patients without clinically significant heart or peripheral vascular

disease, there was no apparent association between peripheral edema and cardiovascular complications such as hypertension or congestive heart failure.
Because there are limited data on congestive heart failure patients with New York Heart Association (NYHA) Class III or IV cardiac status, exercise caution when using pregabalin in these patients.

Weight Gain
Pregabalin treatment may cause weight gain. In pregabalin controlled clinical trials in adult patients of up to 14 weeks, a gain of 7% or more over baseline weight was observed in 9% of pregabalin-treated patients and 2% of placebo-treated patients. Few patients treated with pregabalin (0.3%) withdrew from controlled trials due to weight gain. Pregabalin associated weight gain was related to dose and duration of exposure, but did not appear to be associated with baseline BMI, gender, or age. Weight gain was not limited to patients with edema.
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.
Among diabetic patients, pregabalin-treated patients gained an average of 1.6 kg (range: -16 to 16 kg), compared to an average 0.3 kg (range: -10 to 9 kg) weight gain in placebo patients. In a cohort of 333 diabetic patients who received pregabalin for at least 2 years, the average weight gain was 5.2 kg.
While the effects of pregabalin-associated weight gain on glycemic control have not been systematically assessed, in controlled and longer-term open label clinical trials with diabetic patients, pregabalin treatment did not appear to be associated with loss of glycemic control (as measured by HbA1C).
Some diabetic patients who gain weight on pregabalin treatment may need to adjust hypoglycemic medications.

Abrupt or Rapid Discontinuation
Following abrupt or rapid 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.
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.

Tumorigenic Potential
In standard preclinical *in vivo* lifetime carcinogenicity studies of pregabalin, an unexpectedly high incidence of hemangiosarcoma was identified in two different strains of mice. The clinical significance of this finding is unknown. Clinical experience during pregabalin's pre-marketing development provides no direct means to assess its potential for inducing tumors in humans.
In clinical studies across various patient populations, comprising 6396 patient-years of exposure in patients greater than 12 years of age, new- or worsening-preexisting tumors were reported in 57 patients. Without knowledge of the background incidence and recurrence in similar populations not treated with pregabalin, it is impossible to know whether the incidence seen in these cohorts is or is not affected by treatment.

Ophthalmological Effects
In controlled studies in adult patients, a higher proportion of patients treated with pregabalin reported blurred vision (7%) than did patients treated with placebo (2%), which resolved in a majority of cases with continued dosing. Less than 1% of patients discontinued pregabalin treatment due to vision-related events (primarily blurred vision).
Prospectively planned ophthalmologic testing, including visual acuity testing, formal visual field testing and dilated funduscopic examination, was performed in over 3600 patients. In these patients, visual acuity was reduced in 7% of patients treated with pregabalin, and 5% of placebo-treated patients. Visual field changes were detected in 13% of pregabalin-treated, and 12% of placebo-treated patients. Funduscopic changes were observed in 2% of pregabalin-treated and 2% of placebo-treated patients.
Although the clinical significance of the ophthalmologic findings is unknown, inform patients to notify their physician if changes in vision occur. If visual disturbance persists, consider further assessment. Consider more frequent assessment for patients who are already routinely monitored for ocular conditions.
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.

Creatine Kinase Elevations
Pregabalin treatment was associated with creatine kinase elevations. Mean changes in creatine kinase from baseline to the maximum value were 60 U/L for pregabalin-treated patients and 28 U/L for the placebo patients. In all controlled trials in adult patients across multiple patient populations, 1.5% of patients on pregabalin and 0.7% of placebo patients had a value of creatine kinase at least three times the upper limit of normal. Three pregabalin treated subjects had events reported as rhabdomyolysis in premarketing clinical trials. The relationship between these myopathy events and pregabalin is not completely understood because the cases had documented factors that may have caused or contributed to these events. Instruct patients 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
Pregabalin treatment was associated with a decrease in platelet count. Pregabalin-treated subjects experienced a mean maximal decrease in platelet count of 20 × 103/μL, compared to 11 × 103/μL in placebo patients. In the overall database of controlled trials in adult patients, 2% of placebo patients and 3% of pregabalin patients experienced a potentially clinically significant decrease in platelets, defined as 20% below baseline value and less than 150 × 103/μL. A single pregabalin treated subject developed severe thrombocytopenia with a platelet count less than 20 × 103/μL. In randomized controlled trials, pregabalin was not associated with an increase in bleeding-related adverse reactions.

PR Interval Prolongation
Pregabalin treatment was associated with PR interval prolongation. In analyses of clinical trial ECG data in adult patients, the mean PR interval increase was 3–6 msec at pregabalin doses greater than or equal to 300 mg/day. This mean change difference was not associated with an increased risk of PR increase greater than or equal to 25% from baseline, an increased percentage of subjects with on-treatment PR greater than 200 msec, or an increased risk of adverse reactions of second- or third-degree AV block.
Subgroup analyses did not identify an increased risk of PR prolongation in patients with baseline PR prolongation or in patients taking other PR prolonging medications. However, these analyses cannot be considered definitive because of the limited number of patients in these categories.

Women of childbearing potential/Contraception
Pregabalin use in the first trimester of pregnancy may cause major birth defects in the unborn child. Pregabalin should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the fetus. Women of childbearing potential must use effective contraception during treatment.

Others
Although the effects of discontinuation on the reversibility of renal failure have not been systematically studied, improved renal failure following discontinuation or dose reduction of pregabalin has been reported.
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.
Lactose intolerance
Pregabalin contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
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.

DRUG INTERACTIONS
Since pregabalin is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (<2% of a dose recovered in urine as metabolites), does not inhibit drug metabolism *in vitro*, and is not bound to plasma proteins, it is unlikely to produce, or be subject to, pharmacokinetic interactions.

In vivo studies and population pharmacokinetic analysis
Accordingly, in *in vivo* studies no clinically relevant pharmacokinetic interactions were observed between pregabalin and phenytoin, carbamazepine, valproic acid, lamotrigine, gabapentin, lorazepam, oxycodone or ethanol. Population pharmacokinetic analysis indicated that oral antidiabetics, diuretics, insulin, phenobarbital, tiagabine and topiramate had no clinically significant effect on pregabalin clearance.

Oral contraceptives, norethisterone and/or ethinyl oestradiol
Co-administration of pregabalin with the oral contraceptives norethisterone and/or ethinyl oestradiol does not influence the steady-state pharmacokinetics of either substance.

CNS influencing medical products
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.

In the post-marketing experience, there are reports of respiratory failure, coma and deaths in patients taking pregabalin and other CNS depressant medications including in patients who are substance abusers. There are post-marketing reports of events related to reduced lower gastrointestinal tract function (e.g., intestinal obstruction, paralytic ileus, constipation) when pregabalin was co-administered with medications that have the potential to produce constipation, such as opioid analgesics.

PREGNANCY AND LACTATION
There are no adequate data from the use of pregabalin in pregnant women.
Studies in animals have shown reproductive toxicity .The potential risk for humans is unknown. Pregabalin should not be used during pregnancy unless clearly necessary ((if the benefit to the mother clearly outweighs the potential risk to the foetus).
Data from an observational study, which included more than 2,700 pregnancies exposed to pregabalin based on routinely collected data from administrative and medical registers in Denmark, Finland, Norway, and Sweden, do not suggest substantially increased risks of major congenital malformations, adverse birth outcomes, or abnormal postnatal neurodevelopmental outcomes in pregabalin-exposed pregnancies.

Major congenital malformations
The adjusted prevalence ratios (aPRs) and 95% confidence intervals (CI) in the standard meta-analysis for first-trimester pregabalin monotherapy-exposed vs. unexposed to anti-epileptic drugs was 1.14 (0.96-1.35).

Birth and postnatal neurodevelopmental outcomes
There were no statistically significant findings for stillbirth, low birth weight, preterm birth, small for gestational age, low Apgar score, and microcephaly.
In pediatric population exposed *in utero*, the study did not provide evidence of an increased risk for attention deficit hyperactivity disorder (ADHD), autism spectrum disorders (ASD), and intellectual disabilities.
Studies in animals have shown reproductive toxicity. Pregabalin should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus. Effective contraception must be used in women of child bearing potential.

Lactation
Pregabalin is excreted in the milk of lactating women. As the safety of pregabalin in infants is not known, breast-feeding is not recommended during treatment with pregabalin. A decision must be made whether to discontinue breast-feeding or to discontinue from pregabalin therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

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 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.

SIDE EFFECTS
The most commonly reported adverse reactions are dizziness and somnolence. The most common adverse reactions resulting in discontinuation from pregabalin treatment groups are dizziness and somnolence.
The following adverse events were observed during clinical studies. Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).
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, hypoglycaemia

Psychiatric disorders
Common: Euphoric mood, confusion, irritability, libido decreased, disorientation, insomnia, Depression
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, hypokinesia, parosmia, dysgraphia, ageusia

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: Flushing, hot flushes, hypotension, hypertension, Peripheral coldness

Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness
Rare: Throat tightness, Pulmonary oedema

Gastrointestinal disorders
Common: Vomiting, nausea, constipation, diarrhoea, flatulence, abdominal distension, dry mouth
Uncommon: Gastrooesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral
Rare: Ascites, swollen tongue, pancreatitis, dysphagia

Hepatobiliary disorders
Uncommon: Elevated liver enzymes
Rare: Jaundice
Very rare: Hepatic failure, hepatitis

Skin and subcutaneous tissue disorders
Uncommon: Rash papular, hyperhidrosis, urticaria, pruritus, sweating
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: Ejaculation delayed, sexual dysfunction, breast pain, dysmenorrhoea
Rare: Amenorrhoea, breast discharge, breast enlargement, gynaecomastia

General disorders and administration site conditions
Common: Gait abnormal, fall, feeling drunk, feeling abnormal, fatigue, oedema peripheral, oedema
Uncommon: Chest tightness, asthenia, thirst, pain, chills, generalised oedema, pyrexia, face oedema

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
Discontinuation: After discontinuation of short-term and long-term treatment with pregabalin, withdrawal symptoms may be 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.

The following adverse drug reactions were reported during POST-MARKETING SURVEILLANCE:
Immune system disorder: Uncommon: Hypersensitivity; Rare: Angioedema, allergic reaction.
Nervous system disorders: Very Common: Headache; Uncommon: Loss of consciousness, mental impairment.
Eye disorders: Rare: Keratitis.§
Cardiac disorders: Rare: Congestive heart failure.
Respiratory, thoracic and mediastinal disorders: Rare: Pulmonary oedema.§
Gastrointestinal disorders: Common: Nausea, diarrhoea; Rare: Swollen tongue.
Skin and subcutaneous tissue disorders: Uncommon: Face swelling, pruritus.
Renal and urinary disorders: Rare: Urinary retention.
Reproductive system and breast disorders: Rare: Gynaecomastia.§
General disorders and administration site conditions: Uncommon: Malaise.
§Adverse drug reaction frequency estimated using "The Rule of 3".

SYMPTOMS AND TREATMENT OF OVERDOSE:
Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans
There is limited experience with overdose of pregabalin. The highest reported accidental overdose of pregabalin during the clinical development program was 8000 mg, and there were no notable clinical consequences.
In the post-marketing experience, the most commonly reported adverse events observed when pregabalin was taken in overdose included affective disorder, somnolence, confusional state, depression, agitation and restlessness. Seizures were also reported.
Treatment or Management of Overdose
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).

STORAGE CONDITION:
Store below 30°C.
Keep in cool, dry place away from sunlight.

Keep out of reach of children.

PRESENTATION
For 75 mg & 150mg: Alu/Clear PVC/PVDC blister pack of 10 Capsules

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