1.3 Product Information
1.3.1 Summary of product characteristics (SmPC)
1. Name of the medicinal product: PREGABALIN CAPSULES BP 75 MG

2. Qualitative and quantitative composition:
Each capsule contains:
Pregabalin BP 75 mg
Excipients Q.S.
Approved colour used in empty capsule shell.

Excipients with known effect: Not available

3. Pharmaceutical form: Capsules
Description: Red coloured cap and white coloured body of capsule size 2 containing white powder.

4. Clinical Particulars
4.1 Therapeutic indications
PREGABALIN CAPSULES BP 75 MG is indicated for the treatment of peripheral and central neuropathic pain in adults.
Epilepsy
PREGABALIN CAPSULES BP 75 MG is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.
Generalised anxiety disorder
PREGABALIN CAPSULES BP 75 MG is indicated for the treatment of Generalised Anxiety Disorder (GAD) in adults

4.2 Posology and method of administration
Posology
Route: Oral
The dose range is 150 to 600 mg per day given in either two or three divided doses.

Neuropathic pain
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.
Epilepsy
Pregabalin treatment can be started with 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 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 150 mg per day. Based on individual patient response and tolerability, the dose may be increased to 300 mg per day after 1 week. Following an additional week, the dose may be increased to 450 mg per day. The maximum dose of 600 mg per day may be achieved after an additional week.

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 patients with compromised renal function must be individualised according to creatinine clearance (CLcr), as indicated in Table 1.
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 hour haemodialysis treatment (see Table 1).
Table 1. Pregabalin dose adjustment based on renal function

Creatinine clearance (CL_{cr}) (mL/min)	Total pregabalin daily dose *		Dose regimen
	Starting dose (mg/day)	Maximum dose (mg/day)	
≥ 60	150	600	BID 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[+]

TID = Three divided doses
BID = Two divided doses
* 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 (see section 5.2).

Paediatric population
The safety and efficacy of NEUROLIEF 75 in children below the age of 12 years and in adolescents (12-17 years of age) have not been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

Elderly population
Elderly patients may require a dose reduction of pregabalin due to a decreased renal function (see patients with renal impairment).

Method of administration
PREGABALIN CAPSULES BP 75 MG may be taken with or without food.
PREGABALIN CAPSULES BP 75 MG is for oral use only.

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

4.4 Special warnings and precautions for use
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.

Severe cutaneous adverse reactions (SCARs)

SCARs, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported rarely in association with pregabalin treatment. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, pregabalin should be withdrawn immediately and an alternative treatment considered (as appropriate).

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.

Vision-related effects

In controlled trials, a higher proportion of patients treated with pregabalin reported blurred vision than did patients treated with placebo which resolved in a majority of cases with continued dosing. In the clinical studies where ophthalmologic testing was conducted, the incidence of visual acuity reduction and visual field changes was greater in pregabalin-treated patients than in placebo-treated patients; the incidence of fundoscopic changes was greater in placebo-treated patients.

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 antiepileptic medicinal products, once seizure control with pregabalin in the add-on situation has been reached, in order to reach monotherapy on pregabalin.

Congestive heart failure

There have been post-marketing reports of congestive heart failure in some patients receiving pregabalin. These reactions are mostly seen in elderly cardiovascular compromised patients during pregabalin treatment for a neuropathic indication. Pregabalin should be used with caution in these patients. Discontinuation of pregabalin may resolve the reaction.

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.

Respiratory depression

There have been reports of severe respiratory depression in relation to pregabalin use. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment, concomitant use of CNS depressants and the elderly may be at higher risk of experiencing this severe adverse reaction. Dose adjustments may be necessary in these patients.

Suicidal ideation and behaviour

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled studies of anti-epileptic

drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known.
Patients should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Discontinuation of pregabalin treatment should be considered in case of suicidal ideation and behaviour.

Concomitant use with opioids

Caution is advised when prescribing pregabalin concomitantly with opioids due to risk of CNS depression.

Withdrawal symptoms

After discontinuation of short-term and long-term treatment with pregabalin, withdrawal symptoms have been observed. The following symptoms have been reported: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, nervousness, depression, suicidal ideation, pain, convulsion, hyperhidrosis and dizziness. The occurrence of withdrawal symptoms following discontinuation of pregabalin may indicate drug dependence. The patient should be informed about this at the start of the treatment. If pregabalin should be discontinued, it is recommended this should be done gradually over a minimum of 1 week independent of the indication.
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.

4.5 Interaction with other medicinal products and other forms of interaction

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.

Central nervous system influencing medical products

Pregabalin may potentiate the effects of ethanol and lorazepam. In the postmarketing experience, there are reports of respiratory failure, coma and deaths in patients taking pregabalin and opioids and/or 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.

4.6 Pregnancy and Lactation

Pregnancy

Studies in animals have shown reproductive toxicity.

Pregabalin has been shown to cross the placenta in rats. Pregabalin may cross the human placenta.

Major congenital malformations

Data from a Nordic observational study of more than 2700 pregnancies exposed to pregabalin in the first trimester showed a higher prevalence of major congenital malformations (MCM) among the paediatric population (live or stillborn) exposed to pregabalin compared to the unexposed population (5.9% vs. 4.1%).

PREGABALIN CAPSULES BP 75 MG 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 in 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.

Fertility

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

4.7 Effects on ability to drive and use machines

PREGABALIN CAPSULES BP 75 MG may have minor or moderate influence on the ability to drive and use machines. **PREGABALIN CAPSULES BP 75 MG** 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.

4.8 Undesirable effects

The pregabalin clinical programme involved over 8900 patients exposed to pregabalin, of whom over 5600 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 12 % 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 table 2 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 (≥ 1/10,000 to <1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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 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	 Neutropenia
Immune system disorders Uncommon Rare	 *Hypersensitivity* *Angioedema, allergic reaction*
Metabolism and nutrition disorders Common Uncommon	 Appetite increased Anorexia, hypoglycaemia
Psychiatric disorders Common Uncommon Rare Not known	 Euphoric mood, confusion, irritability, disorientation, insomnia, libido decreased Hallucination, panic attack, restlessness, agitation, depression, depressed mood, elevated mood, *aggression,* mood swings, depersonalisation, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy Disinhibition, suicidal behaviour, suicidal ideation *Drug dependence*
Nervous system disorders Very Common Common Uncommon Rare	 Dizziness, somnolence, headache Ataxia, coordination abnormal, tremor, dysarthria, amnesia, memory impairment, disturbance in attention, paraesthesia, hypoaesthesia, sedation, balance disorder, lethargy 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* *Convulsions,* parosmia, hypokinesia, dysgraphia, *Parkinsonism*
Eye disorders Common Uncommon Rare	 Vision blurred, diplopia Peripheral vision loss, visual disturbance, eye swelling, visual field defect, visual acuity reduced, eye pain, asthenopia, photopsia, dry eye, lacrimation increased, eye irritation *Vision loss, keratitis*, oscillopsia, altered visual depth perception, mydriasis, strabismus, visual brightness

Ear and labyrinth disorders Common Uncommon	 Vertigo Hyperacusis
Cardiac disorders Uncommon Rare	 Tachycardia, atrioventricular block first degree, sinus bradycardia, *congestive heart failure* *QT prolongation*, sinus tachycardia, sinus arrhythmia
Vascular disorders Uncommon	 Hypotension, hypertension, hot flushes, flushing, peripheral coldness
Respiratory, thoracic and mediastinal disorders Uncommon Rare Not known	 Dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness *Pulmonary oedema* , throat tightness Respiratory depression
Gastrointestinal disorders Common Uncommon Rare	 Vomiting, *nausea*, constipation, *diarrhoea*, flatulence, abdominal distension, dry mouth Gastrooesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral Ascites, pancreatitis, *swollen tongue*, dysphagia
Hepatobiliary disorders Uncommon Rare Very rare	 Elevated liver enzymes* Jaundice Hepatic failure, hepatitis
Skin and subcutaneous tissue disorders Uncommon Rare	 Rash papular, urticaria, hyperhidrosis, *pruritus* *Toxic Epidermal Necrolysis, Stevens Johnson syndrome*, cold sweat
Musculoskeletal and connective tissue disorders Common Uncommon Rare	 Muscle cramp, arthralgia, back pain, pain in limb, cervical spasm Joint swelling, myalgia, muscle twitching, neck pain , muscle stiffness Rhabdomyolysis
Renal and urinary disorders Uncommon Rare	 Urinary incontinence, dysuria Renal failure, oliguria, *urinary retention*
Reproductive system and breast disorders Common Uncommon Rare	 Erectile dysfunction Sexual dysfunction, ejaculation delayed, dysmenorrhoea, breast pain Amenorrhoea, breast discharge, breast enlargement, *gynaecomastia*
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 Uncommon Rare	 Weight increased Blood creatine phosphokinase increased, blood glucose increased, platelet count decreased, blood creatinine increased, blood potassium decreased, weight decreased 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. The following symptoms have been reported: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, convulsions, nervousness, depression, suicidal ideation, pain, hyperhidrosis and dizziness. These symptoms may indicate drug 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.

4.9 Overdose

In cases of suspected overdose symptomatic and supportive therapy should be given as appropriate, which should include ECG and blood potassium monitoring.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, other antiepileptics,

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 (α_2-δ protein) of voltage-gated calcium channels in the central nervous system.

Clinical efficacy and safety

Neuropathic Pain

Efficacy has been shown in trials in diabetic neuropathy, post herpetic neuralgia and spinal cord injury. Efficacy has not been studied in other models of neuropathic pain.

Pregabalin has been studied in 10 controlled clinical trials of up to 13 weeks with twice a day dosing (BID) and up to 8 weeks with three times a day (TID) dosing. Overall, the safety and efficacy profiles for BID and TID dosing regimens were similar.

In clinical trials up to 12 weeks for both peripheral and central neuropathic pain, a reduction in pain was seen by week 1 and was maintained throughout the treatment period.

In controlled clinical trials in peripheral neuropathic pain 35 % of the pregabalin treated patients and 18 % of the patients on placebo had a 50 % improvement in pain score. For patients not experiencing somnolence, such an improvement was observed in 33 % of patients treated with pregabalin and 18 % of patients on placebo. For patients who experienced somnolence the responder rates were 48 % on pregabalin and 16 % on placebo.

In the controlled clinical trial in central neuropathic pain 22 % of the pregabalin treated patients and 7 % of the patients on placebo had a 50 % improvement in pain score.

Epilepsy

Adjunctive Treatment

Pregabalin has been studied in 3 controlled clinical trials of 12 week duration with either BID or 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.

Paediatric population

The efficacy and safety of pregabalin as adjunctive treatment for epilepsy in paediatric patients below the age of 12 and adolescents has not been established. The adverse events observed in a pharmacokinetic and tolerability study that enrolled patients from 3 months to 16 years of age (n=65) with partial onset seizures were similar to those observed in adults. Results of a 12 week placebo controlled study of 295 paediatric patients aged 4 to 16 years and a 14-day placebo-controlled study of 175 paediatric patients aged 1 month to younger than 4 years of age performed to evaluate the efficacy and safety of pregabalin as adjunctive therapy for the treatment of partial onset seizures and two 1 year open label safety studies in 54 and 431 paediatric patients respectively from 3 months to 16 years of age with epilepsy indicate that the adverse events of pyrexia and upper respiratory infections were observed more frequently than in adult studies of patients with epilepsy.

In the 12 week placebo controlled study, paediatric patients (4 to 16 years of age) were assigned to pregabalin 2.5 mg/kg/day (maximum, 150 mg/day), pregabalin 10 mg/kg/day (maximum, 600 mg/day), or placebo. The percentage of subjects with at least a 50% reduction in partial onset seizures as compared to baseline was 40.6% of subjects treated with pregabalin 10 mg/kg/day (p=0.0068 versus placebo), 29.1% of subjects treated with pregabalin 2.5 mg/kg/day (p=0.2600 versus placebo) and 22.6% of those receiving placebo.

In the 14-day placebo-controlled study, paediatric patients (1 month to younger than 4 years of age) were assigned to pregabalin 7 mg/kg/day, pregabalin 14 mg/kg/day, or placebo. Median 24-hour seizure frequencies at baseline and at the final visit were 4.7 and 3.8 for pregabalin 7 mg/kg/day, 5.4 and 1.4 for pregabalin 14 mg/kg/day, and 2.9 and 2.3 for placebo, respectively. Pregabalin 14 mg/kg/day significantly reduced the log-transformed partial onset seizure frequency versus placebo (p=0.0223); pregabalin 7 mg/kg/day did not show improvement relative to placebo.

In a 12-week placebo-controlled study in subjects with Primary Generalized Tonic-Clonic (PGTC) seizures 219 subjects (aged 5 to 65 years, of which 66 were aged 5 to 16 years) were assigned to pregabalin 5 mg/kg/day (maximum 300mg/day), 10 mg/kg/day (maximum 600 mg/day) or placebo as adjunctive therapy. The percentage of subjects with at least a 50% reduction in PGTC seizure rate was 41.3%, 38.9% and 41.7% for pregabalin 5 mg/kg/day, pregabalin 10mg/kg/day and placebo respectively.

Monotherapy (newly diagnosed patients)

Pregabalin has been studied in 1 controlled clinical trial of 56 week duration with BID dosing. 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.

Generalised Anxiety Disorder

Pregabalin has been studied in 6 controlled trials of 4-6 week 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 (4-8 week duration) 52 % of the pregabalin treated patients and 38 % of the patients on placebo had at least a 50 % improvement in HAM-A total score from baseline to endpoint.

In controlled trials, a higher proportion of patients treated with pregabalin reported blurred vision than did patients treated with placebo which resolved in a 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 4.8 % of placebo-treated patients. Visual field changes were detected in 12.4 % of pregabalin-treated, and 11.7 % of placebo-treated patients. Funduscopic changes were observed in 1.7 % of pregabalin-treated and 2.1 % of placebo-treated patients.

5.2 Pharmacokinetic properties

Absorption & Bioavailability

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.

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, 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 (see section 5.2 Renal impairment). Dose adjustment in patients with reduced renal function or undergoing haemodialysis is necessary.

Special populations

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.

Paediatric population

Pregabalin pharmacokinetics were evaluated in paediatric patients with epilepsy (age groups: 1 to 23 months, 2 to 6 years, 7 to 11 years and 12 to 16 years) at dose levels of 2.5, 5, 10 and 15 mg/kg/day in a pharmacokinetic and tolerability study.

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 Cmax and AUC parameters increased in a linear manner with increasing dose within each age group. The AUC was lower by 30% in paediatric patients below a weight of 30 kg due to an increased body weight adjusted clearance of 43% for these patients in comparison to patients weighing ≥30 kg.

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.

Pregabalin pharmacokinetics in patients younger than 3 months old have not been.

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

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 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.

5.3 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.

6. Pharmaceutical particulars

6.1 List of excipients

Microcrystalline cellulose, Sodium Starch Glycolate (Primojel), Colloidal anhydrous silica, Magnesium stearate, EHG Capsule Size '2' Cap – Red Body- White

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C in a dry and dark place.
Keep all medicines out of reach of children.

6.5 Nature and contents of container

Primary packing: 10 Capsules in an ALU-PVC blister.

Secondary packing: 3 Blisters are packed in a printed carton along with leaflet.

Tertiary packing: 10 Cartons are packed in a shrink. Such 30 Shrinks are packed in a 5 Ply shipper sealed with BOPP tape & strap with strapping roll.

6.6 Special precautions for disposal and other handling

Not applicable

Manufactured By:
Name : M/S FLOURISH PHARMA

ADDRESS :Of 24E, GOA-IDC,Daman Ind. Estate, Somnath Dabhel, (U.T) -396 215 India.

Email: flourish.pharma@yahoo.com

Number: +91 98211 53413

Marketed By;

Name : M/S KNOX PHARMACEUTICAL LTD

ADDRESS : Plot 22, Green Estate, Amuwo Odofin Festac, Lagos State. Nigeria.

Email: knoxpharmacy91@gmail.com
Tel: +234-814 983 2596

PACKAGE LEAFLET

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

PREGABALIN TABLET 300MG

(PREGABALIN TABLET 300MG)

Pharmaceutical form:

Solid

Route of administration:

Oral

Composition:

Each uncoated tablet contains	
Pregabalin BP	300 mg
Excipients	q.s.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you. • Keep this leaflet. You may need to read it again. • If you have any further questions, ask your doctor, pharmacist or nurse. • This medicine has been prescribed for you only.

Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours. • If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What PREGABALIN 300mg TABLET is and what it is used for and what it is used for

PREGABALIN 300mg TABLET is a medication that contains pregabalin as its active ingredient. It belongs to a group of medicines called antiepileptic drugs, although it is also used to treat certain types of long-lasting pain. PREGABALIN 300mg TABLET is prescribed to:

- Treat various forms of epilepsy in adults and children aged 4 years and older.
- Manage neuropathic pain, such as diabetic neuropathy, post-herpetic neuralgia, and peripheral neuropathic pain.
- Provide relief from generalized anxiety disorder (GAD) in adults.

2. What you need to know before you take PREGABALIN 300mg TABLET ?

Before you start taking PREGABALIN 300mg TABLET, please read this section carefully. It contains important information about potential risks and precautions:

Do not take PREGABALIN 300mg TABLET:

- If you are allergic to pregabalin or any of the other ingredients in this medicine.
- If you have severe heart failure.
- If you are under 18 years old for the treatment of epilepsy or generalized anxiety disorder.
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Warnings and precautions:

- Inform your doctor if you have ever had thoughts of harming yourself or suicide.
- PREGABALIN may cause dizziness and drowsiness. Avoid activities requiring mental alertness, such as driving or operating machinery, until you know how this medication affects you.
- PREGABALIN can lead to weight gain. You should monitor your weight regularly and inform your doctor if you notice significant weight gain.
- If you have kidney problems, please inform your doctor as the dose may need to be adjusted.

3.How to take PREGABALIN 300mg TABLET

Follow your doctor's instructions precisely. Do not change the dose without consulting them. Swallow the tablet whole with water. Do not chew or crush it.

PREGABALIN 300mg TABLET can be taken with or without food.

The usual starting dose for most conditions is 150mg daily, which can be increased to 300mg daily within 1 week based on your response and doctor's recommendations.

If you have kidney problems, your doctor may adjust the dose accordingly.

For Adults:

- **Dosage:** Follow your doctor's instructions precisely regarding the dosage. Do not change the dose without consulting them.
- **Administration:** Swallow the PREGABALIN 300mg TABLET whole with a full glass of water. Do not chew or crush the tablet.
- **Timing:** PREGABALIN 300mg TABLET can be taken with or without food. You can choose a time that is convenient for you, but it is recommended to take it at the same time every day for consistency.
- **Starting Dose:** The usual starting dose for most conditions in adults is 150mg daily, usually divided into two or three doses. Your doctor will determine the appropriate starting dose based on your medical condition.
- **Dose Adjustment:** Your doctor may increase the dose to 300mg daily within one week if needed and based on your individual response to the medication. This may involve taking multiple 150mg tablets
- **Kidney Problems:** If you have kidney problems, your doctor may adjust the dose according to your kidney function. It is essential to inform your doctor about any kidney issues you may have.

For Children (Aged 4 years and older):

- **Dosage:** The dosage for children is determined by the child's weight and age, and it should be prescribed by a pediatrician. Follow the pediatrician's instructions precisely and do not change the dose without consulting them.
- **Administration:** Children should swallow the PREGABALIN 300mg TABLET whole with a full glass of water. The tablet should not be chewed or crushed.
- **Timing:** The timing of administration for children should be as directed by the pediatrician. It may vary based on the child's condition.
- **Starting Dose:** The starting dose for children will be determined by the pediatrician based on the child's specific medical condition and weight. It may not necessarily be 150mg.
- **Dose Adjustment:** The pediatrician will monitor the child's response to the medication and may adjust the dose as needed.
- **Kidney Problems:** If the child has kidney problems, it is crucial to inform the pediatrician, as the dose may need to be adjusted accordingly.

4. Possible side effects

Like all medicines, PREGABALIN 300mg TABLET can cause side effects, although not everybody will experience them. Common side effects may include dizziness, somnolence, headache, weight gain, and blurred vision. Refer to the package insert for a comprehensive list of side effects and their details. If you experience any unusual or severe side effects, contact your doctor immediately.

Common Side Effects (may affect up to 1 in 10 people):

1. **Dizziness:** Some individuals may experience dizziness, which can affect their balance and coordination. This side effect often occurs when you start taking PREGABALIN and may improve over time.
2. **Somnolence (Sleepiness):** PREGABALIN can cause drowsiness or sleepiness, which may impact your ability to concentrate or operate heavy machinery. Avoid activities requiring mental alertness until you know how this medication affects you.
3. **Headache:** Headaches are a common side effect and are usually mild to moderate in intensity.
4. **Weight Gain:** Some individuals may experience weight gain while taking PREGABALIN. It's important to monitor your weight regularly and discuss any significant changes with your doctor.
5. **Blurred Vision:** Blurred vision is another possible side effect. If you experience this, avoid tasks that require clear vision, such as driving, until your vision returns to normal.

Less Common Side Effects (may affect up to 1 in 100 people):

6. **Dry Mouth:** Dry mouth or xerostomia can occur as a less common side effect. **Rare Side Effects (may affect up to 1 in 1,000 people):**
7. **Allergic Reactions:** Rarely, allergic reactions such as skin rash, itching, swelling of the face or tongue, and difficulty breathing may occur. Seek immediate medical attention if you experience any signs of an allergic reaction.
8. **Mood Changes:** Some individuals may experience mood changes, including agitation, confusion, irritability, or depression.
9. **Muscle Pain or Weakness:** Muscle pain or weakness has been reported as a rare side effect.
10. **Loss of Coordination:** In some cases, a loss of coordination or unsteadiness may occur.
11. **Memory Problems:** Memory problems or difficulty with concentration have been reported in rare cases.
12. **Unusual Bleeding or Bruising:** Rarely, PREGABALIN may lead to unusual bleeding or bruising.

5 How to store PREGABALIN 300mg TABLET

1. Keep this medicine out of the sight and reach of children:

- Store PREGABALIN 300mg TABLET in a location where it is inaccessible to children. Consider using a locked medicine cabinet or a high shelf.

2. Store below 25°C (77°F):

- PREGABALIN 300mg TABLET should be stored at a temperature below 25°C (77°F). This is to ensure that the medication remains stable and effective. Avoid exposure to excessive heat or cold, and do not store it in the refrigerator unless directed otherwise by your healthcare provider.

3. Protect from light and moisture:

- Store the medication in its original packaging or container to protect it from light and moisture. Direct sunlight, humidity, and moisture can potentially affect the stability and effectiveness of the tablets.

- Avoid storing PREGABALIN 300mg TABLET in a bathroom or any area with high humidity, as moisture can degrade the medication.

4. Do not use this medicine after the expiry date stated on the packaging:

- Check the packaging for the expiry date, which is the date after which the medication should not be used. Do not use PREGABALIN 300mg TABLET if it has passed its expiry date, as it may not be safe or effective.

- Dispose of any expired medication properly, following local regulations for medication disposal. Do not throw it in the trash or flush it down the toilet unless instructed to do so by your local authorities or healthcare provider.

It's important to store medications properly to maintain their effectiveness and ensure your safety. If you have any questions about the storage of PREGABALIN 300mg TABLET or if you are unsure about any aspect of its storage, consult your pharmacist or healthcare provider for guidance.

6. Contents of the pack and other information

What it looks like PREGABALIN 300mg TABLET are White coloured caplet shaped uncoated tablet having breakline on one side and plain on othwsr side of each tablet.

Ingredients Each Pregabalin tablet contains:

• 300mg of Pregabalin as active ingredient.

• Starch, Lactose, Talc,Microcrystallinre cellulose, Sodium starch glycollate, PVPK-30 , sodium benzoate , Aerosil, LMagnesium stearate, Colloidal Anhydrous silica, Sodium lauryl sulphate and Purified Talc are excipients .

Tablets are available in 10 x 15 Tablets pack packed in carton along with insert

Manufacturer
FLOURISH PHARMA
24E ,GOA-IDC, Daman IND. Estate, Daman
(U.T.) India

Marketed by :
KNOX PHARMACEUTICAL NIGERIA
LIMITED.