PREGABALIN CAPSULES 300 MG

Summary of Product Characteristics (SmPC)

1. Name of the medicinal product

Pregabalin Capsules 300 mg

2. Qualitative and quantitative composition

Each hard gelatin capsule contains:

Pregabalin BP 300 mg

Excipients q.s.

Approved colour used in capsule shell

3. Pharmaceutical form

Hard Gelatin Capsule

4. Clinical particulars

4.1. Therapeutic indications

Pregabalin capsules are indicated for:

- Management of neuropathic pain associated with diabetic peripheral neuropathy
- Management of postherpetic neuralgia
- Adjunctive therapy for the treatment of partial-onset seizures in patients 17 years of age and older
- Management of fibromyalgia
- Management of neuropathic pain associated with spinal cord injury

Pediatric use information is approved for Pfizer's LYRICA (pregabalin) Capsules and Oral Solution products. However, due to Pfizer's marketing exclusivity rights, this drug product is not labeled with that pediatric information.

4.2 Posology and method of administration

2.1 Important Administration Instructions

Pregabalin capsules are given orally with or without food.

When discontinuing pregabalin, taper gradually over a minimum of 1 week.

Because pregabalin is eliminated primarily by renal excretion, adjust the dose in adult patients with reduced renal function .

2.2 Neuropathic Pain Associated with Diabetic Peripheral Neuropathy in Adults

The maximum recommended dose of pregabalin capsule is 100 mg three times a day (300 mg/day) in patients with creatinine clearance of at least 60 mL/min. Begin dosing at 50 mg

three times a day (150 mg/day). The dose may be increased to 300 mg/day within 1 week based on efficacy and tolerability.

Although pregabalin was also studied at 600 mg/day, there is no evidence that this dose confers additional significant benefit and this dose was less well tolerated. In view of the dose-dependent adverse reactions, treatment with doses above 300 mg/day is not recommended.

2.3 Postherpetic Neuralgia in Adults

The recommended dose of pregabalin capsule is 75 mg to 150 mg two times a day, or 50 mg to 100 mg three times a day (150mg/day to 300 mg/day) in patients with creatinine clearance of at least 60 mL/min. Begin dosing at 75 mg two times a day, or 50 mg three times a day (150 mg/day). The dose may be increased to 300 mg/day within 1 week based on efficacy and tolerability.

Patients who do not experience sufficient pain relief following 2 to 4 weeks of treatment with 300 mg/day, and who are able to tolerate pregabalin, may be treated with up to 300 mg two times a day, or 200 mg three times a day (600 mg/day). In view of the dose-dependent adverse reactions and the higher rate of treatment discontinuation due to adverse reactions, reserve dosing above 300 mg/day for those patients who have on-going pain and are tolerating 300 mg daily.

2.4 Adjunctive Therapy for Partial-Onset Seizures in Patients 17 Years of Age and Older

The recommended dosage for adult patients 17 years of age and older are included in Table 1. Administer the total daily dosage orally in two or three divided doses as indicated in Table 1. Based on clinical response and tolerability, dosage may be increased, approximately weekly.

Table 1: Recommended Dosage for Adult Patients 17 Years and Older

Age and Body Weight	**Recommended Initial Dosage**	**Recommended Maximum Dosage**	**Frequency of Administration**
Adults (17 years and older)	150 mg/day	600 mg/day	2 or 3 divided doses

Both the efficacy and adverse event profiles of pregabalin have been shown to be dose-related.

The effect of dose escalation rate on the tolerability of pregabalin has not been formally studied.

The efficacy of adjunctive pregabalin in patients taking gabapentin has not been evaluated

in controlled trials. Consequently, dosing recommendations for the use of pregabalin with gabapentin cannot be offered.

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2.5 Management of Fibromyalgia in Adults

The recommended dose of pregabalin capsules for fibromyalgia is 300 mg/day to 450 mg/day. Begin dosing at 75 mg two times a day (150 mg/day). The dose may be increased to 150 mg two times a day (300 mg/day) within 1 week based on efficacy and tolerability. Patients who do not experience sufficient benefit with 300 mg/day may be further increased to 225 mg two times a day (450 mg/day). Although pregabalin was also studied at 600 mg/day, there is no evidence that this dose confers additional benefit and this dose was less well tolerated. In view of the dose-dependent adverse reactions, treatment with doses above 450 mg/day is not recommended.

2.6 Neuropathic Pain Associated with Spinal Cord Injury in Adults

The recommended dose range of pregabalin capsules for the treatment of neuropathic pain associated with spinal cord injury is 150 mg/day to 600 mg/day. The recommended starting dose is 75 mg two times a day (150 mg/day). The dose may be increased to 150 mg two times a day (300 mg/day) within 1 week based on efficacy and tolerability. Patients who do not experience sufficient pain relief after 2 to 3 weeks of treatment with 150 mg two times a day and who tolerate pregabalin capsules may be treated with up to 300 mg two times a day.

2.7 Dosing for Adult Patients with Renal Impairment

In view of dose-dependent adverse reactions and since pregabalin is eliminated primarily by renal excretion, adjust the dose in adult patients with reduced renal function. The use of pregabalin in pediatric patients with compromised renal function has not been studied.

Base the dose adjustment in patients with renal impairment on creatinine clearance (CLcr), as indicated in Table 2. To use this dosing table, an estimate of the patient's CLcr in mL/min is needed. CLcr in mL/min may be estimated from serum creatinine (mg/dL) determination using the Cockcroft and Gault equation:

Next, refer to the Dosage and Administration section to determine the recommended total daily dose based on indication, for a patient with normal renal function (CLcr greater than or equal to 60 mL/min). Then refer to Table 2 to determine the corresponding renal adjusted dose.

(For example: A patient initiating pregabalin therapy for postherpetic neuralgia with normal renal function (CLcr greater than or equal to 60 mL/min), receives a total daily dose of 150 mg/day pregabalin. Therefore, a renal impaired patient with a CLcr of 50 mL/min would receive a total daily dose of 75 mg/day pregabalin administered in two or three divided doses.)

For patients undergoing hemodialysis, adjust the pregabalin daily dose based on renal function. In addition to the daily dose adjustment, administer a supplemental dose immediately following every 4-hour hemodialysis treatment .

Table 2. Pregabalin Dosage Adjustment Based on Renal Function

Creatinine Clearance (CLcr) (mL/min)	**Total Pregabalin Daily Dose (mg/day) ***				**Dose Regimen**
Greater than or equal to 60	150	300	450	600	BID or TID
30–60	75	150	225	300	BID or TID
15–30	25–50	75	100–150	150	QD or BID
Less than 15	25	25–50	50–75	75	QD
Supplementary dosage following hemodialysis (mg) †					
Patients on the 25 mg QD regimen: take one supplemental dose of 25 mg or 50 mg					
Patients on the 25 mg – 50 mg QD regimen: take one supplemental dose of 50 mg or 75 mg					
Patients on the 50 mg – 75 mg QD regimen: take one supplemental dose of 75 mg or 100 mg					
Patients on the 75 mg QD regimen: take one supplemental dose of 100 mg or 150 mg					

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.

4.3 Contraindications

regabalin capsule 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.

4.4 Special warnings and precautions for use

5.1 Angioedema

There have been postmarketing 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 capsules immediately in patients with these symptoms.

Exercise caution when prescribing pregabalin capsules 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.

5.2 Hypersensitivity

There have been postmarketing 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 capsules immediately in patients with these symptoms.

5.3 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 to 100 years) in the clinical trials analyzed.

Table 3 shows absolute and relative risk by indication for all evaluated AEDs.

Table 3. Risk by indication for Antiepileptic Drrugs 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.

5.4 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.

5.5 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.

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.

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5.6 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.

5.7 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.

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.

5.8 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).

5.9 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 premarketing development provides no direct means to assess its potential for inducing tumors in humans.

In clinical studies across various patient populations, comprising 6,396 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.

5.10 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 3,600 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.

5.11 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.

5.12 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.

5.13 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 msec to 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.

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 (less than 2% of a dose recovered in urine as metabolites), and does not bind to plasma proteins, its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions or protein binding displacement. In vitro and in vivo studies showed that pregabalin is unlikely to be involved in significant pharmacokinetic drug interactions. Specifically, there are no pharmacokinetic interactions between pregabalin and the following antiepileptic drugs: carbamazepine, valproic acid, lamotrigine, phenytoin, phenobarbital, and topiramate. Important pharmacokinetic interactions would also not be expected to occur between pregabalin and commonly used antiepileptic drugs .

Pharmacodynamics

Multiple oral doses of pregabalin were co-administered with oxycodone, lorazepam, or ethanol. Although no pharmacokinetic interactions were seen, additive effects on cognitive and gross motor functioning were seen when pregabalin was co-administered with these drugs. No clinically important effects on respiration were seen.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception Women of childbearing potential have to use effective contraception during treatment . 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%). The risk of MCM among the paediatric population exposed to pregabalin in the first trimester was slightly higher compared to unexposed population (adjusted prevalence ratio and 95% confidence interval: 1.14 (0.96-1.35)), and compared to population exposed to lamotrigine (1.29 (1.01–1.65)) or to duloxetine (1.39 (1.07–1.82)). The analyses on specific malformations showed higher risks for malformations of the nervous system, the eye, orofacial clefts, urinary malformations and genital malformations, but numbers were small and estimates imprecise. Pregabalin should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the foetus). Breast-feeding Pregabalin is excreted into human milk. The

effect of pregabalin on newborns/infants is unknown. A decision must be made whether to discontinue breast-feeding or to discontinue pregabalin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. Fertility There are no clinical data on the effects of pregabalin on female fertility. In a clinical trial to assess the effect of pregabalin on sperm motility, healthy male subjects were exposed to pregabalin at a dose of 600 mg/day. After 3 months of treatment, there were no effects on sperm motility. A fertility study in female rats has shown adverse reproductive effects. Fertility studies in male rats have shown adverse reproductive and developmental effects. The clinical relevance of these findings is unknown.

4.7 Effects on ability to drive and use machines

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 9 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 program involved over 8,900 patients exposed to pregabalin, of whom over 5,600 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 postmarketing experience are included in italics in the list below. Table 2. Pregabalin Adverse Drug Reactions System Organ Class Adverse drug reactions Infections and infestations Common Nasopharyngitis Blood and lymphatic system disorders Uncommon Neutropaenia Immune system disorders Uncommon Hypersensitivity Rare Angioedema, allergic reaction Metabolism and nutrition disorders Common Appetite increased Uncommon Anorexia, hypoglycaemia Psychiatric disorders Common Euphoric mood, confusion, irritability, disorientation, insomnia, libido decreased Uncommon Hallucination, panic attack, restlessness, agitation, depression, depressed mood, elevated mood, aggression, mood swings, depersonalisation, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy Rare Disinhibition, suicidal behaviour, suicidal ideation 10 System Organ Class Adverse drug reactions Not known Drug dependence Nervous system disorders Very Common Dizziness, somnolence, headache Common Ataxia, coordination abnormal, tremor, dysarthria, amnesia, memory impairment, disturbance in attention, paraesthesia, hypoaesthesia, sedation, balance disorder, lethargy Uncommon Syncope, stupor, myoclonus, loss of consciousness, psychomotor hyperactivity, dyskinesia, dizziness postural, intention tremor, nystagmus, cognitive disorder, mental impairment, speech disorder, hyporeflexia, hyperaesthesia, burning sensation, ageusia, malaise Rare Convulsions, parosmia, hypokinesia, dysgraphia, parkinsonism Eye disorders Common Vision blurred, diplopia Uncommon Peripheral vision loss, visual disturbance, eye swelling, visual field defect, visual acuity reduced, eye pain, asthenopia, photopsia, dry eye, lacrimation increased, eye irritation Rare Vision loss, keratitis, oscillopsia, altered visual depth perception, mydriasis, strabismus, visual brightness Ear and labyrinth disorders Common Vertigo Uncommon Hyperacusis Cardiac disorders Uncommon Tachycardia, atrioventricular block first degree, sinus bradycardia, congestive heart failure Rare QT prolongation, sinus tachycardia, sinus arrhythmia Vascular disorders Uncommon Hypotension, hypertension, hot flushes, flushing, peripheral coldness Respiratory, thoracic and mediastinal disorders Uncommon Dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness Rare Pulmonary oedema, throat tightness, Not known Respiratory depression Gastrointestinal disorders Common Vomiting, nausea, constipation, diarrhoea, flatulence, abdominal distension, dry mouth Uncommon Gastrooesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral Rare Ascites, pancreatitis, swollen tongue, dysphagia Hepatobiliary disorders 11 System Organ Class Adverse drug reactions Uncommon Elevated liver enzymes* Rare Jaundice Very rare Hepatic failure, hepatitis Skin

and subcutaneous tissue disorders Uncommon Rash papular, urticaria, hyperhidrosis, pruritus Rare Toxic epidermal necrolysis, Stevens Johnson syndrome, cold sweat Musculoskeletal and connective tissue disorders Common Muscle cramp, arthralgia, back pain, pain in limb, cervical spasm Uncommon Joint swelling, myalgia, muscle twitching, neck pain, muscle stiffness Rare Rhabdomyolysis Renal and urinary disorders Uncommon Urinary incontinence, dysuria Rare Renal failure, oliguria, urinary retention Reproductive system and breast disorders Common Erectile dysfunction Uncommon Sexual dysfunction, ejaculation delayed, dysmenorrhoea, breast pain Rare Amenorrhoea, breast discharge, breast enlargement, gynaecomastia General disorders and administration site conditions Common Oedema peripheral, oedema, gait abnormal, fall, feeling drunk, feeling abnormal, fatigue Uncommon Generalised oedema, face oedema, chest tightness, pain, pyrexia, thirst, chills, asthenia Investigations Common Weight increased Uncommon Blood creatine phosphokinase increased, blood glucose increased, platelet count decreased, blood creatinine increased, blood potassium decreased, weight decreased Rare White blood cell count decreased * Alanine aminotransferase increased (ALT) and aspartate aminotransferase increased (AST). After discontinuation of short-term and long-term treatment with pregabalin withdrawal symptoms have been observed . The following symptoms have been reported: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, convulsions, nervousness, depression, 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. Paediatric population 12 The pregabalin safety profile observed in fivepaediatric studies in patients with partial seizures with or without secondary generalisation 12-week efficacy and safety study in patients 4 to 16 years of age, n=295; 14-day efficacy and safety study in patients 1 month to younger than 4 years of age, n=175; pharmacokinetic and tolerability study, n=65; and two 1 year open label follow on safety studies, n=54 and n=431) was similar to that observed in the adult studies of patients with epilepsy. The most common adverse events observed in the 12-week study with pregabalin treatment were somnolence, pyrexia, upper respiratory tract infection, increased appetite, weight increased, and nasopharyngitis. The most common adverse events observed in the 14-day study with pregabalin treatment were somnolence, upper respiratory tract infection, and pyrexia. Reporting of suspected adverse reactions Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the

benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans

In the postmarketing experience, the most commonly reported adverse events observed with pregabalin when taken in overdose include reduced consciousness, depression/anxiety, confusional state, agitation, and restlessness. Seizures and heart block have also been reported. Deaths have been reported in the setting of lone pregabalin overdose and in combination with other CNS depressants.

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. Contact a Certified Poison Control Center for up-to-date information on the management of overdose with pregabalin.

Pregabalin can be removed by hemodialysis. Standard hemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours).

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-epileptics, other anti-epileptics ATC code: N03AX16 The active substance, pregabalin, is a gamma-aminobutyric acid analogue [(S) -3-(aminomethyl) -5-methylhexanoic acid]. Mechanism of action Pregabalin binds to an auxiliary subunit (α2-δ protein) of voltage-gated calcium channels in the central nervous system, Clinical efficacy and safety Neuropathic pain Efficacy has been shown in 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% 13 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 300 mg/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 10 mg/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. 14 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

Pregabalin steady-state pharmacokinetics are similar in healthy volunteers, patients with epilepsy receiving anti-epileptic drugs and patients with chronic pain. Absorption Pregabalin is rapidly absorbed when administered in the fasted state, with peak plasma concentrations occurring within 1 hour following both single and multiple dose administration. Pregabalin oral bioavailability is estimated to be ≥ 90% and is independent of dose. Following repeated administration, steady state is achieved within 24 to 48 hours. The rate of pregabalin absorption is decreased when given with food resulting in a decrease in Cmax by approximately 25-30% and a delay in tmax to approximately 2.5 hours. However, administration of pregabalin with food has no clinically significant effect on the extent of pregabalin absorption. Distribution 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. Gender 15 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. 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 studied. 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 Excipients

6.1 List of excipients

S. NO	INGREDIENTS	
1.	MAGNESIUM STEARATE	BP
2.	TALCUM	BP
3.	LACTOSE MONOHYDRATE	BP
4.	DRIED STARCH	BP
5.	EMPTY HARD GELATIN CAPSULES (RED PLUS & PEARL WHITE) "0" SIZE	-

6.2 Incompatibilities

None known

6.3 Shelf life

3 years

6.4 Special precaution for storage

Store in original packaging in order to protect from light.

6.5 Nature contents of container

10 x 15 capsules in a carton

6.6 Instruction for use handling and disposal

Keep out of reach of children

7. Marketing authorization holder

Manufacturer

Alpa Laboratories Limited

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