1. NAME OF THE MEDICINAL PRODUCT

EPIBALIN 75 (Pregabalin Hard Capsule 75mg)
EPIBALIN 150 (Pregabalin Hard Capsule 150mg)
EPIBALIN 300 (Pregabalin Hard Capsule 300mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

75 mg
Each hard capsule contains 75 mg of pregabalin.

150 mg
Each hard capsule contains 150 mg of pregabalin.

300 mg
Each hard capsule contains 300 mg of pregabalin.

3. PHARMACEUTICAL FORM

75 mg hard capsules
White to off white colour granular powder filled in size "4" hard gelatin capsules with white opaque body imprinted "PGBN" and light blue opaque cap imprinted "75" with black ink

150 mg hard capsules
White to off white colour granular powder filled in size "2" hard gelatin capsules with white opaque body imprinted "PGBN" and light blue opaque cap imprinted "150" with black ink

300 mg hard capsules
White to off white colour granular powder filled in size "0" hard gelatin capsules with white opaque body imprinted "PGBN" and light blue opaque cap imprinted "300" with black ink

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

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

4.2 Posology and method of administration

The dose range is 150 to 600 mg per day given in either two or three divided doses. Pregabalin may be taken with or without food.

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

Fibromyalgia
The usual dose range for most patients is 300 to 450 mg per day given in two divided doses. Some patients may derive additional benefit at 600 mg per day. Dosing should begin at 75 mg two times a day (150 mg/day) and may

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

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

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

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

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

Patients with renal impairment

Dosage reduction in patients with compromised renal function must be individualised according to creatinine clearance (CL_{cr}) (see Section **5.2 Pharmacokinetic properties,** Pharmacokinetics in special patient groups, *Renal impairment*), as indicated in Table 1 determined using the following formula:

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

For patients receiving hemodialysis, the pregabalin daily dose should be adjusted based on renal function. In addition to the daily dose, a supplementary dose should be given immediately following every 4-hour haemodialysis treatment (see Table 1).

Table 1. Pregabalin Dosage Adjustment Based on Renal Function

	Total Pregabalin Daily Dose*		
Creatinine Clearance (CL_{cr}) (mL/min)	Starting Dose (mg/day)	Maximum Dose (mg/day)	Dose Regimen
≥60	150	600	BID or TID
≥30 - <60	75	300	BID or TID
≥15 - <30	25 – 50	150	QD or BID
<15	25	75	QD
Supplementary dosage following haemodialysis (mg)			
	25	100	Single dose^{+}

TID = Three divided doses.
BID = Two divided doses.
QD = Single daily dose.
*Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose.
$^{+}$Supplementary dose is a single additional dose.

Use in patients with hepatic impairment

No dosage adjustment is required for patients with hepatic impairment (see Section **5.2 Pharmacokinetic properties,** Pharmacokinetics in special patient groups, *Hepatic impairment*).

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

The safety and effectiveness of pregabalin in pediatric patients below the age of 12 years and adolescents has not been established.

The use in children is not recommended.

Use in the elderly (over 65 years of age)

Elderly patients may require a dose reduction of pregabalin due to decreased renal function (see Section **5.2 Pharmacokinetic properties,** Pharmacokinetics in special patient groups, *Elderly (over 65 years of age)*).

4.3 Contraindications

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

4.4 Special warnings and precautions for use

4.4.1 Angioedema

There have been post-marketing reports of angioedema in patients during initial and chronic treatment with pregabalin. Specific symptoms included swelling of the face, mouth (tongue, lips, and gums), and neck (throat and larynx). There were reports of life-threatening angioedema with respiratory compromise requiring emergency treatment. Discontinue pregabalin immediately in patients with these symptoms.

Exercise caution when prescribing pregabalin to patients who have had a previous episode of angioedema. In addition, patients who are taking other drugs associated with angioedema (e.g., angiotensin converting enzyme inhibitors [ACE-inhibitors]) may be at increased risk of developing angioedema.

4.4.2 Hypersensitivity

There have been post-marketing reports of hypersensitivity in patients shortly after initiation of treatment with pregabalin. Adverse reactions included skin redness, blisters, hives, rash, dyspnea, and wheezing. Discontinue pregabalin immediately in patients with these symptoms.

4.4.3 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 (5-100 years) in the clinical trials analyzed.

Table 2 shows absolute and relative risk by indication for all evaluated AEDs.

Table 2. Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

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

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

Anyone considering prescribing pregabalin or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

4.4.4 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.

4.4.5 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 and could increase the occurrence of accidental injury (fall) in the elderly population.

In the pregabalin controlled trials in adult patients, dizziness was experienced by 30% of pregabalin- treated patients compared to 8% of placebo-treated patients; somnolence was experienced by 23% of pregabalin-treated patients compared to 8% of placebo-treated patients. Dizziness and somnolence generally began shortly after the initiation of pregabalin therapy and occurred more frequently at higher doses. Dizziness and somnolence were the adverse reactions most frequently leading to withdrawal (4% each) from controlled studies. In pregabalin-treated patients reporting these adverse

reactions in short-term, controlled studies, dizziness persisted until the last dose in 30% and somnolence persisted until the last dose in 42% of patients (see Section **4.5 Interaction with other medicinal products and other forms of interaction**).

There have also been post-marketing reports of loss of consciousness, confusion and mental impairment. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medication.

Pregabalin is not known to be active at receptor sites associated with drugs of abuse. Cases of misuse, abuse and dependence have been reported in the post-marketing database. As with any CNS active drug, carefully evaluate patients for history of drug abuse and/or psychiatric disorders. Caution should be applied when considering pregabalin use in patients with current substance abuse or a history of substance abuse, who are at higher risk for pregabalin abuse (see Section **5.1 Pharmacodynamic properties**).

Patients treated with pregabalin should be observed for signs and symptoms of pregabalin misuse, abuse or dependence (e.g. development of tolerance, dose escalation, drug-seeking behavior).

4.4.6 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 capsule, some patients reported symptoms including insomnia, nausea, headache, anxiety, hyperhidrosis, and diarrhea.

If pregabalin capsule is discontinued, taper the drug gradually over a minimum of 1 week rather than discontinue the drug abruptly.

4.4.7 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.

Although there has been no causal relationship identified between exposure to pregabalin and congestive heart failure, there has been post-marketing reports of congestive heart failure in some patients receiving pregabalin. In short-term trials of patients without clinically significant heart or peripheral vascular disease, there was no apparent association between peripheral edema and cardiovascular complications such as hypertension or congestive heart failure.

Because there are limited data on congestive heart failure patients with New York Heart Association (NYHA) Class III or IV cardiac status, exercise caution when using pregabalin in these patients.

4.4.8 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 (see Section **4.4 Special warnings and precautions for use**).

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 HbA_{1C}).

Some diabetic patients who gain weight on pregabalin treatment may need to adjust hypoglycemic medications.

4.4.9 Abrupt or Rapid Discontinuation

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

Convulsions, including status epilepticus and grand mal convulsions, may occur during pregabalin use or shortly after discontinuing pregabalin.

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

There are insufficient data for the withdrawal of concomitant antiepileptic medicinal products, once seizure control with pregabalin in the add-on situation has been reached, in order to reach monotherapy on pregabalin.

4.4.10 Tumorigenic Potential

In standard preclinical *in vivo* lifetime carcinogenicity studies of pregabalin, an unexpectedly high incidence of hemangiosarcoma was identified in two different strains of mice. The clinical significance of this finding is unknown. Clinical experience during pregabalin's pre-marketing development provides no direct means to assess its potential for inducing tumors in humans.

In clinical studies across various patient populations, comprising 6396 patient-years of exposure in patients greater than 12 years of age, new- or worsening-preexisting tumors were reported in 57 patients. Without knowledge of the background incidence and recurrence in similar populations not treated with pregabalin, it is impossible to know whether the incidence seen in these cohorts is or is not affected by treatment.

4.4.11 Ophthalmological Effects

In controlled studies in adult patients, a higher proportion of patients treated with pregabalin reported blurred vision (7%) than did patients treated with placebo (2%), which resolved in a majority of cases with continued dosing. Less than 1% of patients discontinued pregabalin treatment due to vision- related events (primarily blurred vision).

Prospectively planned ophthalmologic testing, including visual acuity testing, formal visual field testing and dilated funduscopic examination, was performed in over 3600 patients. In these patients, visual acuity was reduced in 7% of patients treated with pregabalin, and 5% of placebo-treated patients. Visual field changes were detected in 13% of pregabalin-treated, and 12% of placebo-treated patients. Funduscopic changes were observed in 2% of pregabalin-treated and 2% of placebo-treated patients.

Although the clinical significance of the ophthalmologic findings is unknown, inform patients to notify their physician if changes in vision occur. If visual disturbance persists, consider further assessment. Consider more frequent assessment for patients who are already routinely monitored for ocular conditions.

In the post-marketing experience, visual adverse reactions have also been reported, including loss of vision, visual blurring or other changes of visual acuity, many of which were transient. Discontinuation of pregabalin may result in resolution or improvement of these visual symptoms.

4.4.12 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.

4.4.13 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 $20 \times 10^3/\mu L$, compared to $11 \times 10^3/\mu L$ 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 $150 \times 10^3/\mu L$. A single pregabalin treated subject developed severe thrombocytopenia with a platelet count less than $20 \times 10^3/\mu L$. In randomized controlled trials, pregabalin was not associated with an increase in bleeding-related adverse reactions.

4.4.14 PR Interval Prolongation

Pregabalin treatment was associated with PR interval prolongation. In analyses of clinical trial ECG data in adult patients, the mean PR interval increase was 3–6 msec at pregabalin doses greater than or equal to 300 mg/day. This mean change difference was not associated with an increased risk of PR increase greater than or equal to 25% from baseline, an increased percentage of subjects with on- treatment PR greater than 200 msec, or an increased risk of adverse reactions of second- or third- degree AV block.

Subgroup analyses did not identify an increased risk of PR prolongation in patients with baseline PR prolongation or in patients taking other PR prolonging medications. However, these analyses cannot be considered definitive because of the limited number of patients in these categories.

4.4.15 Women of childbearing potential/Contraception

Pregabalin use in the first trimester of pregnancy may cause major birth defects in the unborn child. Pregabalin should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the fetus. Women of childbearing potential must use effective contraception during treatment (see Section **4.6 Fertility, pregnancy and lactation**).

4.4.16 Others

Although the effects of discontinuation on the reversibility of renal failure have not been systematically studied, improved renal failure following discontinuation or dose reduction of pregabalin has been reported.

Misuse, abuse potential or dependence

Cases of misuse, abuse and dependence have been reported. Caution should be exercised in patients with a history of substance abuse and the patient should be monitored for symptoms of pregabalin misuse, abuse or dependence (development of tolerance, dose escalation, drug seeking behaviour have been reported).

Encephalopathy

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

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.

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.

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.

Co-administration of pregabalin with the oral contraceptives norethisterone and/or ethinyl estradiol does not influence the steady-state pharmacokinetics of either substance. Pregabalin may potentiate the effects of ethanol and lorazepam. In controlled clinical trials, multiple oral doses of pregabalin co- administered with oxycodone, lorazepam, or ethanol did not result in clinically important effects on respiration. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone.

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

No specific pharmacodynamic interaction studies were conducted in elderly volunteers.

4.6 Fertility, pregnancy and lactation

There is a limited amount of data on the use of pregabalin in pregnant women.

Data from an observational study, which included more than 2,700 pregnancies exposed to pregabalin based on routinely collected data from administrative and medical registers in Denmark, Finland, Norway, and Sweden, do not suggest substantially increased risks of major congenital malformations, adverse birth outcomes, or abnormal postnatal neurodevelopmental outcomes in pregabalin-exposed pregnancies.

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

Birth and postnatal neurodevelopmental outcomes

There were no statistically significant findings for stillbirth, low birth weight, preterm birth, small for gestational age, low Apgar score, and microcephaly.

In pediatric population exposed *in utero*, the study did not provide evidence of an increased risk for attention deficit hyperactivity disorder (ADHD), autism spectrum disorders (ASD), and intellectual disabilities.

Studies in animals have shown reproductive toxicity. Pregabalin should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus. Effective contraception must be used in women of child bearing potential (see Section **4.4 Special warnings and precautions for use**).
Lactation

Pregabalin is excreted in the milk of lactating women (see Section **5.2 Pharmacokinetic properties**). As the safety of pregabalin in infants is not known, breast-feeding is not recommended during treatment with pregabalin. A decision must be made whether to discontinue breast-feeding or to discontinue from pregabalin therapy taking into

account the benefit of breast feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Selected adverse drug reactions that were treatment related in the pooled analysis of clinical trials are listed in the table below by System Organ Class (SOC). The frequency of these terms has been based on all-causality adverse drug reactions in the clinical trial data set (very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100) and rare (<1/1000)).

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

Table 3. Adverse Drug Reactions from Clinical Trial Experience

System Organ Class	**Adverse Drug Reactions**
Infections and infestations	
Common	Nasopharyngitis
Blood and lymphatic system disorders	
Uncommon	Neutropenia
Metabolism and nutrition disorders	
Common	Appetite increased
Uncommon	Anorexia, hypoglycemia
Psychiatric disorders	
Common	Euphoric mood, confusion, irritability, depression, disorientation, insomnia, libido decreased
Uncommon	Hallucination, restlessness, agitation, depressed mood, elevated mood, mood swings, depersonalization, abnormal dreams, word finding difficulty, libido increased, anorgasmia
Rare	Panic attack, disinhibition, apathy
Nervous system disorders	
Very Common	Dizziness, somnolence
Common	Ataxia, coordination abnormal, tremor, dysarthria, amnesia, memory impairment, disturbance in attention, paraesthesia, hypoesthesia, sedation, balance disorder, lethargy
Uncommon	Syncope, myoclonus, psychomotor hyperactivity, dyskinesia, dizziness postural, intention tremor, nystagmus, cognitive disorder, speech disorder, hyporeflexia, hyperaesthesia, burning sensation
Rare	Stupor, parosmia, hypokinesia, ageusia, dysgraphia
Eye disorders	
Common	Vision blurred, diplopia
Uncommon	Peripheral vision loss, visual disturbance, eye swelling, visual field defect, visual acuity reduced, eye pain, asthenopia, photopsia, dry eye, lacrimation increased, eye irritation
Rare	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
Rare	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
Rare	Throat tightness, nasal dryness
Gastrointestinal disorders	
Common	Vomiting, constipation, flatulence, abdominal distension, dry mouth
Uncommon	Gastrooesophageal reflux disease, salivary hypersecretion, hypoesthesia oral
Rare	Ascites, pancreatitis, dysphagia
Skin and subcutaneous tissue disorders	
Uncommon	Rash papular, urticaria, sweating
Rare	Cold sweat, Stevens-Johnson syndrome
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
Reproductive system and breast disorders	
Uncommon	Erectile dysfunction, sexual dysfunction, ejaculation delayed, dysmenorrhoea
Rare	Breast pain, amenorrhoea, breast discharge, breast enlargement
General disorders and administration site conditions	
Common	Oedema peripheral, oedema, gait abnormal, fall, feeling drunk, feeling abnormal, fatigue
Uncommon	Generalised oedema, chest tightness, pain, pyrexia, thirst, chills, asthenia
Investigations	
Common	Weight increased
Uncommon	Blood creatine phosphokinase increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood glucose increased, platelet count decreased, blood potassium decreased, weight decreased
Rare	White blood cell count decreased, blood creatinine increased

The following adverse drug reactions were reported during POST-MARKETING SURVEILLANCE:

Immune system disorder: Uncommon: Hypersensitivity; Rare: Angioedema, allergic reaction.
Nervous system disorders: Very Common: Headache; Uncommon: Loss of consciousness, mental impairment.

Eye disorders: Rare: Keratitis[§]

Cardiac disorders: Rare: Congestive heart failure.

Respiratory, thoracic and mediastinal disorders: Rare: Pulmonary oedema[§]

Gastrointestinal disorders: Common: Nausea, diarrhoea; Rare: Swollen tongue.

Skin and subcutaneous tissue disorders: Uncommon: Face swelling, pruritus; Rare: Stevens- Johnson syndrome.

Renal and urinary disorders: Rare: Urinary retention.

Reproductive system and breast disorders: Rare: Gynaecomastia[§]

General disorders and administration site conditions: Uncommon: Malaise.
[§]Adverse drug reaction frequency estimated using "The Rule of 3".

4.9 Overdose

In overdoses up to 15 g, no unexpected adverse reactions were reported.
In the post-marketing experience, the most commonly reported adverse events observed when pregabalin was taken in overdose included affective disorder, somnolence, confusional state, depression, agitation and restlessness. Seizures were also reported.

Treatment of pregabalin overdose should include general supportive measures and may include haemodialysis if necessary (see Section **4.2 Posology and method of administration**, Table 1).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other analgesics and antipyretics, ATC code: N02BF02.

The active substance, pregabalin, is a gamma-aminobutyric acid analogue ((S)-3-(aminomethyl)-5- methylhexanoic acid).

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

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

Clinical experience

Neuropathic pain

Efficacy has been shown in studies in diabetic neuropathy and post-herpetic neuralgia. Efficacy has not been studied in other models of neuropathic pain.

Pregabalin has been studied in 9 controlled clinical studies of up to 13 weeks with twice a day dosing and up to 8 weeks with three times a day dosing. Overall, the safety and efficacy profiles for twice a day and three times a day dosing regimens were similar.

In clinical trials up to 13 weeks, a reduction in pain was seen by Week 1 and was maintained throughout the treatment period.

In controlled clinical trials 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.

Fibromyalgia

Pregabalin as monotherapy has been studied in 5 placebo-controlled studies, three of 12 weeks fixed-dose

duration, one of 7 weeks fixed-dose duration, and a 6-month study demonstrating long-term efficacy. Pregabalin treatment in all fixed-dose studies produced a significant reduction in pain associated with fibromyalgia at doses from 300 to 600 mg/day (BID).
In the three 12-week fixed-dose studies, 40% of pregabalin-treated patients experienced a 30% or more improvement in pain score versus 28% of the patients on placebo; 23% of treated patients experienced a 50% or more improvement in pain score versus 15% of the patients on placebo.

Pregabalin produced significantly superior global assessment scores via the Patient Global Impression of Change (PGIC) in the three 12-week fixed-dose studies as compared to placebo treatment (41% patients feeling very much or much improved on pregabalin versus 29% on placebo). As measured by Fibromyalgia Impact Questionnaire (FIQ), pregabalin produced a statistically significant improvement in function versus placebo treatment in 2 out of the 3 fixed-dose studies in which it was evaluated.

Pregabalin treatment produced significant improvements in patient-reported sleep outcomes in the 4 fixed-dose studies as measured by Medical Outcomes Study Sleep Scale (MOS-SS) Sleep disturbance subscale, MOS-SS overall sleep problem index, and the daily sleep quality diary.

In the 6-month study, improvement in pain, global assessment (PGIC), function (FIQ total score) and sleep (MOS-SS Sleep disturbance subscale) were maintained for pregabalin-treated patients for a significantly longer period compared to placebo.

Pregabalin 600 mg/day showed an additional improvement in patient-reported sleep outcomes as compared to 300 and 450 mg/day; mean effects on pain, global assessment, and FIQ were similar at 450 and 600 mg/day, although the 600 mg per day dose was less well tolerated.

A 15-week, placebo-controlled trial was conducted with 107 pediatric patients with fibromyalgia, ages 12 through 17 years, at pregabalin total daily doses of 75-450 mg per day. The primary efficacy endpoint of change from baseline to Week 15 in mean pain intensity (derived from an 11 point numeric rating scale) showed numerically greater improvement for the pregabalin treated patients compared to placebo treated patients, but did not reach statistical significance. The most frequently observed adverse reactions in the clinical trial included dizziness, nausea, headache, weight increased, and fatigue. The overall safety profile in adolescents was similar to that observed in adults with fibromyalgia.

Epilepsy

Pregabalin has been studied in 3 controlled clinical studies of 12-week duration with either twice a day dosing or three times a day dosing. Overall, the safety and efficacy profiles for twice a day and three times a day dosing regimens were similar.

A reduction in seizure frequency was observed by Week 1.
Generalised anxiety disorder

Pregabalin has been studied in 6 controlled studies of 4 to 6 weeks duration, an elderly study of 8 weeks 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 weeks 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.

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 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 Pharmacokinetic properties,** Pharmacokinetics in special patient groups, *Renal impairment*).

Dosage adjustment in patients with reduced renal function or undergoing hemodialysis is necessary (see Section **4.2 Posology and method of administration**, Table 1).

Linearity/Non-linearity

Pregabalin pharmacokinetics are linear over the recommended daily dose range. Inter-subject pharmacokinetic variability for pregabalin is low (<20%). Multiple dose pharmacokinetics are predictable from single-dose data. Therefore, there is no need for routine monitoring of plasma concentrations of pregabalin.

Pharmacokinetics in special patient groups

Gender

Clinical trials indicate that gender does not have a clinically significant influence on the plasma concentrations of pregabalin.

Renal impairment

Pregabalin clearance is directly proportional to creatinine clearance. In addition, pregabalin is effectively removed from plasma by hemodialysis (following a 4-hour hemodialysis treatment plasma pregabalin concentrations are reduced by approximately 50%). Because renal elimination is the major elimination pathway, dosage reduction in patients with renal impairment and dosage supplementation following hemodialysis is necessary (see Section **4.2 Posology and method of administration**, Table 1).

Hepatic impairment

No specific pharmacokinetic studies were carried out in patients with impaired liver function. Since pregabalin does not undergo significant metabolism and is excreted predominantly as unchanged drug in the urine, impaired liver function would not be expected to significantly alter pregabalin plasma concentrations.

Elderly (over 65 years of age)

Pregabalin clearance tends to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with decreases in creatinine clearance associated with increasing age. Reduction of pregabalin dose may be required in patients who have age related compromised renal function (see Section **4.2 Posology and method of administration**, Table 1).

Breast-feeding mothers

The pharmacokinetics of 150 mg pregabalin given every 12 hours (300 mg daily dose) was evaluated in 10 lactating women who were at least 12 weeks postpartum. Lactation had little to no influence on pregabalin pharmacokinetics. Pregabalin was excreted into breast milk with average steady-state concentrations approximately 76% of those in maternal plasma. The estimated average daily infant dose of pregabalin from breast milk (assuming mean milk consumption of 150 mL/kg/day) was
0.31 mg/kg/day, which on a mg/kg basis would be approximately 7% of the maternal dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsules content:
Mannitol (E421)
Talc

Capsules shell:
Gelatin
Titanium dioxide (E171)
FD & C Blue 2
Purified water

Printing Ink:
Shellac (E904)
Black iron oxide (E172)
Ammonia Solution, concentrated (E527)
Potassium hydroxide (E525)
Propylene glycol (E1520)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please refer outer carton for expiry date.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Alu-Clear PVC/Aclar blister containing 10 hard capsules. Such 3 blister packs are further packed in a printed carton along with package insert

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7. MANUFACTURER

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Formulations Division Unit-II,
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8. PRODUCT REGISTRATION HOLDER

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9. DATE OF REVISION

Aug 2026