Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product

Pregabalin Sustained Release Tablets 50 mg (CABALIN 50 SR)

2. Qualitative and quantitative composition

Each film coated sustained release tablet contains:
Pregabalin BP 50 mg

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet
White, round, biconvex, plain on both side film coated tablets.

4. Clinical particulars

4.1 Therapeutic indications

PREGABALIN SUSTAINED RELEASE TABLET is indicated for the management of: Neuropathic pain associated with diabetic peripheral neuropathy.

Postherpetic neuralgia
Efficacy of PREGABALIN SUSTAINED RELEASE TABLET has not been established for the management of fibromyalgia or as adjunctive therapy for adult patients with partial onset seizures.

4.2 Posology and method of administration

Important Dosage and Administration Instructions
PREGABALIN SUSTAINED RELEASE TABLET should be administered once daily after an evening meal.
PREGABALIN SUSTAINED RELEASE TABLET should be swallowed whole and should not be split, crushed, or chewed.
When discontinuing PREGABALIN SUSTAINED RELEASE TABLET, taper gradually over a minimum of 1 week.
Instruct patients that if they miss taking their dose of PREGABALIN SUSTAINED RELEASE TABLET after an evening meal, then they should take their usual dose of PREGABALIN SUSTAINED RELEASE TABLET prior to bedtime following a snack. If they miss taking the dose of PREGABALIN SUSTAINED RELEASE TABLET prior to bedtime, then they should take their usual dose of PREGABALIN SUSTAINED RELEASE TABLET following a morning meal. If they miss taking the dose of PREGABALIN SUSTAINED RELEASE TABLET following the morning meal, then they should take their usual dose of PREGABALIN SUSTAINED RELEASE TABLET at the usual time that evening following an evening meal.

Neuropathic Pain Associated with Diabetic Peripheral Neuropathy
Begin dosing at 165 mg once daily and increase to 330 mg once daily within 1 week based on individual patient response and tolerability. The maximum recommended dose of PREGABALIN SUSTAINED RELEASE TABLET is 330 mg once daily.
Although PREGABALIN was studied at 600 mg/day, there was no evidence that this

dose conferred additional significant benefit and this dose was less well tolerated. In view of the dose-dependent adverse reactions with PREGABALIN, treatment with doses above 330 mg/day is not recommended for PREGABALIN SUSTAINED RELEASE TABLET.

Postherpetic Neuralgia

Begin dosing at 165 mg once daily and increase to 330 mg once daily within 1 week based on individual patient response and tolerability.

Patients who do not experience sufficient pain relief following 2 to 4 weeks of treatment with 330 mg once daily and who are able to tolerate PREGABALIN SUSTAINED RELEASE TABLET, may be treated with up to 660 mg once daily. In view of the dose-dependent adverse reactions and the higher rate of treatment discontinuation due to adverse reactions, dosing above 330 mg/day should be reserved only for those patients who have on-going pain and are tolerating 330 mg daily. The maximum recommended dose of PREGABALIN SUSTAINED RELEASE TABLET is 660 mg once daily.

Conversion From PREGABALIN Capsules or Oral Solution to PREGABALIN SUSTAINED RELEASE TABLET

When switching from PREGABALIN-to-PREGABALIN SUSTAINED RELEASE TABLET on the day of the switch, instruct patients to take their morning dose of PREGABALIN as prescribed and initiate PREGABALIN SUSTAINED RELEASE TABLET therapy after an evening meal.

Table 1: Conversion from PREGABALIN Capsules or Oral Solution to PREGABALIN SUSTAINED RELEASE TABLET

PREGABALIN Total Daily Dose (dosed 2 or 3 times daily)	PREGABALIN SUSTAINED RELEASE TABLET Dose (dosed once a day)
75 mg/daily	82.5 mg/day
150 mg/daily	165 mg/day
225 mg/daily	247.5 mg/day[a]
300 mg/daily	330 mg/day
450 mg/daily	495 mg/day[b]
600 mg/daily	660 mg/day[c]
[a]247.5 mg = 3 x 82.5 mg tablets taken once a day. [b]495 mg = 3 x 165 mg tablets taken once a day. [c]660 mg = 2 x 330 mg tablets taken once a day.	

Patients With Renal Impairment

Use of PREGABALIN SUSTAINED RELEASE TABLET is not recommended for patients with creatinine clearance (CLcr) less than 30 mL/min or who are undergoing hemodialysis. Those patients should receive PREGABALIN.

In view of dose-dependent adverse reactions and because pregabalin is eliminated primarily by renal excretion, adjust the dose in patients with reduced renal function. Base the dose adjustment in patients with renal impairment on CLcr, as indicated in Table 2. To use the dosing tables, 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:

Males: $\frac{\text{(weight in kg) x (140 – age)}}{}$

(72) x serum creatinine (mg/100 mL)

Females: (0.85) x (above value)

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 SUSTAINED RELEASE TABLET therapy for postherpetic neuralgia with normal renal function [CLcr greater than or equal to 60 mL/min], receives a single daily dose of 165 mg/day pregabalin. Therefore, a renal impaired patient with a CLcr of 50 mL/min would receive a single daily dose of 82.5 mg.)

Table 2: PREGABALIN SUSTAINED RELEASE TABLET Dosage Adjustment Based on Renal Function

Creatinine Clearance (CLcr) (mL/min)	**Total PREGABALIN SUSTAINED RELEASE TABLET Daily Dose (mg/day)**				**Dose Regimen**
greater than or equal to 60	165	330	495[a]	660[b]	Once a day
30-60	82.5	165	247.5[c]	330	Once a day
less than 30/hemodialysis	Dose with PREGABALIN				

[a]495 mg = 3 x 165 mg tablets taken once a day.
[b]660 mg = 2 x 330 mg tablets taken once a day.
[c] 247.5 mg = 3 x 82.5 mg tablets taken once a day.

4.3 Contraindications

PREGABALIN SUSTAINED RELEASE TABLET 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

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

Hypersensitivity Reactions

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

Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including pregabalin, the active ingredient in PREGABALIN SUSTAINED RELEASE TABLET, 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% among16,029 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 beyond24 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 3 shows absolute and relative risk by indication for all evaluated AEDs.

Table 3: 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 SUSTAINED RELEASE TABLET must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. 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.
Inform patients, their caregivers, and families that PREGABALIN SUSTAINED RELEASE TABLET can increase the risk of suicidal thoughts and behavior and advise them of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Report behaviors of concern immediately to healthcare providers.

Peripheral Edema

PREGABALIN SUSTAINED RELEASE TABLET 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 for pain indications, the incidence of peripheral edema for patients receiving PREGABALIN SUSTAINED RELEASE TABLET in the single-blind phase was 5.3% of patients. In controlled clinical trials for pain indications, 0.8% of PREGABALIN SUSTAINED RELEASE TABLET patients withdrew due to peripheral edema during the single-blind phase.
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, monitor patients for the development of edema when co- administering PREGABALIN SUSTAINED RELEASE TABLET 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, monitor these patients for possible exacerbation of congestive heart failure symptoms when using PREGABALIN SUSTAINED RELEASE TABLET.

Dizziness and Somnolence

PREGABALIN SUSTAINED RELEASE TABLET may cause dizziness and somnolence. Inform patients that PREGABALIN SUSTAINED RELEASE TABLET-related dizziness and somnolence may impair their ability to perform tasks such as driving or operating machinery. Concomitant use of PREGABALIN SUSTAINED RELEASE TABLET with other central nervous system (CNS) depressants may exacerbate these effects.

In the PREGABALIN SUSTAINED RELEASE TABLET controlled trials for pain indications, dizziness was experienced by 24% of PREGABALIN SUSTAINED RELEASE TABLET-treated patients during the single-blind phase; somnolence was experienced by 15.8% of PREGABALIN SUSTAINED RELEASE TABLET-treated patients. Dizziness and somnolence generally began shortly after the initiation of PREGABALIN SUSTAINED RELEASE TABLET therapy and occurred more frequently at higher doses. Dizziness and somnolence were the adverse reactions most frequently leading to withdrawal (2.4%, 1.2% each) during the single-blind phase of the 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.

Weight Gain

PREGABALIN SUSTAINED RELEASE TABLET treatment may cause weight gain. In PREGABALIN SUSTAINED RELEASE TABLET controlled trials for pain indications, weight gain was experienced by 4% of PREGABALIN SUSTAINED RELEASE TABLET-treated patients during the single-blind phase. Adverse events of weight gain were observed in 3.7% of PREGABALIN SUSTAINED RELEASE TABLET-treated patients and 1% of placebo-treated patients during the double-blind phase. In PREGABALIN controlled clinical trials 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. In studies with PREGABALIN, associated weight gain was related to pregabalin 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 with PREGABALIN, 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).

Risks Associated with Abrupt or Rapid Discontinuation

Following abrupt or rapid discontinuation of PREGABALIN SUSTAINED RELEASE TABLET, some patients reported symptoms including, insomnia, nausea, headache, anxiety, and diarrhea. Increased seizure frequency may occur in patients with seizure disorders taking PREGABALIN SUSTAINED RELEASE TABLET for

pain if PREGABALIN SUSTAINED RELEASE TABLET is rapidly discontinued. Taper PREGABALIN SUSTAINED RELEASE TABLET gradually over a minimum of 1 week rather than discontinuing the drug abruptly. The efficacy of PREGABALIN SUSTAINED RELEASE TABLET as adjunctive therapy for adult patients with partial onset seizures has not been established.

Tumorigenic Potential

In standard preclinical in vivo lifetime carcinogenicity studies of pregabalin, an unexpectedly high incidence of hemangiosarcoma was identified in 2 different strains of mice. The clinical significance of this finding is unknown. Clinical experience during premarketing development of PREGABALIN provides no direct means to assess its potential for inducing tumors in humans.

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

Ophthalmological Effects

In controlled studies for pain indications, 4.8% of patients treated with PREGABALIN SUSTAINED RELEASE TABLET in the single-blind phase reported blurred vision, which resolved in a majority of cases with continued dosing. Less than 1% of patients discontinued PREGABALIN SUSTAINED RELEASE TABLET treatment due to vision-related events (primarily blurred vision). Additionally, 0.7% of PREGABALIN SUSTAINED RELEASE TABLET-treated patients as compared to no placebo-treated patients experienced blurred vision in the double-blind phase. Prospectively planned ophthalmologic testing during the premarketing development of pregabalin, 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 PREGABALIN- treated patients 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.

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 across multiple patient populations, 1.5% of patients on PREGABALIN and 0.7% of placebo patients had a value of creatine kinase at least 3 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 SUSTAINED RELEASE TABLET if myopathy is diagnosed or suspected or if markedly elevated creatine kinase levels occur.

Decreased Platelet Count

Both PREGABALIN SUSTAINED RELEASE TABLET and PREGABALIN treatment were associated with a decrease in platelet count. In the double-blind phase of controlled studies for pain indication, PREGABALIN SUSTAINED RELEASE TABLET-treated patients experienced a median change from baseline in platelet count of 11 x $10^3/mm^2$ (for the PHN population) and 14 x $10^3/mm^2$ (for the FM population) as compared to 1 x $10^3/mm^2$ in placebo-treated patients (for both populations). PREGABALIN-treated patients experienced a mean maximal decrease in platelet count of 20 x $10^3/\mu L$, compared to 11 x $10^3/\mu L$ in placebo patients. In the overall database of controlled trials, 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 x $10^3/\mu L$. A single PREGABALIN- treated subject developed severe thrombocytopenia with a platelet count less than 20 x $10^3/\mu L$. In randomized controlled trials, PREGABALIN or PREGABALIN SUSTAINED RELEASE TABLET were not associated with an increase in bleeding-related adverse reactions.

PR Interval Prolongation

PREGABALIN treatment was associated with PR interval prolongation. In analyses of clinical trial ECG data, 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.

Patient Counseling Information

Advise the patient to read the FDA-approved patient labeling (**Medication Guide**).

Angioedema

Advise patients that PREGABALIN SUSTAINED RELEASE TABLET may cause angioedema, with swelling of the face, mouth (lip, gum, tongue) and neck (larynx and pharynx) that can lead to life- threatening respiratory compromise. Instruct patients to discontinue PREGABALIN SUSTAINED RELEASE TABLET and immediately seek medical care if they experience these symptoms.

Hypersensitivity

Advise patients that PREGABALIN SUSTAINED RELEASE TABLET has been associated with hypersensitivity reactions such as skin redness, blisters, hives, rash, dyspnea, and wheezing. Instruct patients to discontinue PREGABALIN SUSTAINED RELEASE TABLET and immediately seek medical care if they experience these symptoms.

Suicidal Thinking and Behavior

Counsel patients, their caregivers, and families that AEDs, including pregabalin, the active ingredient in PREGABALIN SUSTAINED RELEASE TABLET, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Instruct patients, caregivers, and families to report behaviors of concern immediately to a healthcare provider.

Dizziness and Somnolence

Inform patients that PREGABALIN SUSTAINED RELEASE TABLET may cause dizziness, somnolence, blurred vision, and other CNS signs and symptoms. Accordingly, advise patients not to drive, operate complex machinery, or engage in other hazardous activities until they have gained sufficient experience on PREGABALIN SUSTAINED RELEASE TABLET to gauge whether or not it affects their mental, visual, and/or motor performance adversely.

Weight Gain and Edema

Inform patients that PREGABALIN SUSTAINED RELEASE TABLET may cause edema and weight gain. Advise patients that concomitant treatment with PREGABALIN SUSTAINED RELEASE TABLETand a thiazolidinedione antidiabetic agent may lead to an additive effect on edema and weight gain. Advise patients with preexisting cardiac conditions that this may increase the risk of heart failure.

Abrupt or Rapid Discontinuation

Advise patients to take PREGABALIN SUSTAINED RELEASE TABLET as prescribed. Abrupt or rapid discontinuation may result in insomnia, nausea, headache, anxiety, or diarrhea. Advise patients with seizure disorders that abrupt or rapid discontinuation may increase seizure frequency.

Ophthalmological Effects

Counsel patients that PREGABALIN SUSTAINED RELEASE TABLET may cause visual disturbances. Inform patients that if changes in vision occur, they should notify their physician.

Creatine Kinase Elevations

Instruct patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

CNS Depressants

Inform patients who require concomitant treatment with central nervous system depressants such as opiates or benzodiazepines that they may experience additive CNS side effects, such as somnolence and dizziness.

Alcohol

Advise patients to avoid consuming alcohol while taking PREGABALIN SUSTAINED RELEASE TABLET, as PREGABALIN SUSTAINED RELEASE TABLET may potentiate the impairment of motor skills and sedating effects of alcohol.

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 studies showed that pregabalin is unlikely to be involved in significant pharmacokinetic drug interactions.
The interactions of PREGABALIN SUSTAINED RELEASE TABLET with co-administration of other drugs have not been systematically evaluated. Co-administration of the prokinetic drug erythromycin with PREGABALIN SUSTAINED RELEASE TABLET did not result in any clinically important changes in the pharmacokinetics of PREGABALIN SUSTAINED RELEASE TABLET.
Additional studies have been performed with PREGABALIN. No pharmacokinetic interactions were observed between PREGABALIN and carbamazepine, gabapentin, lamotrigine, oral contraceptive, phenobarbital, phenytoin, topiramate, and valproic acid. A similar lack of pharmacokinetic interactions would be expected to occur with PREGABALIN SUSTAINED RELEASE TABLET.

4.6 Fertility, pregnancy and lactation Pregnancy

There are no adequate data from the use of pregabalin in pregnant women.
Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.

Risk Summary

There are no adequate and well-controlled studies with PREGABALIN SUSTAINED RELEASE TABLET in pregnant women.
However, in animal reproduction studies, increased incidences of fetal structural abnormalities and other manifestations of developmental toxicity, including skeletal malformations, retarded ossification, and decreased fetal body weight were observed in the offspring of rats and rabbits given pregabalin orally during organogenesis, at doses that produced plasma pregabalin exposures (AUC) greater than or equal to 18 times human exposure at the maximum recommended dose (MRD) of 660 mg/day. In an animal development study, lethality, growth retardation, and nervous and reproductive system functional impairment were observed in the offspring of rats given pregabalin during gestation and lactation. The no- effect dose for developmental toxicity was approximately twice the human exposure at MRD. The background risk of major birth defects and miscarriage for the indicated populations are unknown. However, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies. Advise pregnant women of the potential risk to a fetus.

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 potentially hazardous activities until it is known whether this medicinal product affects their ability to perform these activities.

4.8 Undesirable effects

The following adverse reactions are described elsewhere in the labeling:
-Angioedema
-Hypersensitivity Reactions

-Suicidal Behavior and Ideation
-Peripheral Edema
-Dizziness and Somnolence
-Weight Gain
-Ophthalmological Effects
-Creatine Kinase Elevations
-Decreased Platelet Count

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Two randomized placebo-controlled clinical trials were conducted in patients with postherpetic neuralgia and fibromyalgia in which a total of 1242 patients received PREGABALIN SUSTAINED RELEASE TABLET. Both studies were randomized withdrawal design where a 6-week single-blind, dose optimization phase was followed by a 13-week double-blind phase. The most common adverse events leading to discontinuation from the single-blind phase of the study occurring in greater than or equal to 0.3% of patients were dizziness, somnolence, peripheral edema, fatigue, blurred vision, and increased weight. Sixty-four percent of patients experienced adverse events during the single-blind phase, with the most common adverse events occurring in greater than or equal to 4% of patients being dizziness, somnolence, headache, fatigue, peripheral edema, nausea, blurred vision, dry mouth, and weight gain.

Controlled Study in Postherpetic Neuralgia Adverse Reactions Leading to Discontinuation

In a clinical trial in patients with postherpetic neuralgia, 8.9% of patients treated with PREGABALIN SUSTAINED RELEASE TABLET discontinued prematurely during the single-blind phase due to adverse reactions. The most common reasons for discontinuation due to adverse reactions were dizziness (2.1%), somnolence (0.87%), and peripheral edema (0.50%).

Most Common Adverse Reactions

Table 4 lists all adverse reactions, regardless of causality, occurring in greater than or equal to 1% of patients with postherpetic neuralgia who received PREGABALIN SUSTAINED RELEASE TABLET, regardless of the phase of the study.

Table 4: Incidence of Adverse Reactions Reported in Greater Than or Equal to 1% of Subjects in Any Phase of the PREGABALIN SUSTAINED RELEASE TABLET Study in Patients With Postherpetic Neuralgia*

System Organ Class Preferred Term	Single-Blind Phase	Double-Blind Phase	
	PREGABALIN SUSTAINED RELEASE TABLET [N=801] n (%)	PREGABALIN SUSTAINED RELEASE TABLET [N=208] n (%)	Placebo [N=205] n(%)
Ear and labyrinth disorders			
Vertigo	31 (3.9)	2 (1.0)	1 (0.5)

Eye disorders			
Vision blurred	30 (3.7)	1 (0.5)	0
Diplopia	8 (1.0)	1 (0.5)	0
Gastrointestinal disorders			
Dry mouth	30 (3.7)	1 (0.5)	0
Nausea	24 (3.0)	7 (3.4)	0
Constipation	22 (2.7)	0	0
Diarrhea	11 (1.4)	2 (1.0)	1 (0.5)
Vomiting	9 (1.1)	3 (1.4)	1 (0.5)
General disorders and administration site conditions			
Edema peripheral	39 (4.9)	8 (3.8)	1 (0.5)
Fatigue	31 (3.9)	3 (1.4)	2 (1.0)
Edema	3 (0.4)	3 (1.4)	0
Infections and infestations			
Nasopharyngitis	12 (1.5)	3 (1.4)	0
Urinary tract infection	11 (1.4)	3 (1.4)	1 (0.5)
Bronchitis	4 (0.5)	3 (1.4)	2 (1.0)
Respiratory tract infection viral	3 (0.4)	3 (1.4)	1 (0.5)
Sinusitis	3 (0.4)	2 (1.0)	0
Gastroenteritis viral	2 (0.2)	2 (1.0)	0
Investigations			
Weight increased	20 (2.5)	8 (3.8)	2 (1.0)
Alanine aminotransferase increased	2 (0.2)	3 (1.4)	0
Aspartate aminotransferase increased	2 (0.2)	2 (1.0)	0
Musculoskeletal and connective tissue disorders			
Arthralgia	6 (0.7)	2 (1.0)	1 (0.5)
Joint swelling	0	4 (1.9)	0
Nervous system disorders			
Dizziness	137 (17.1)	7 (3.4)	1 (0.5)

Somnolence	91 (11.4)	1 (0.5)	0
Headache	31 (3.9)	4 (1.9)	1 (0.5)
Balance disorder	21 (2.6)	1 (0.5)	0
Reproductive system and breast disorders			
Erectile dysfunction	2 (0.6)	1 (14)	0
Respiratory, thoracic, and mediastinal disorders			
Cough	2 (0.2)	2 (1.0)	1 (0.5)
Skin and subcutaneous tissue disorders			
Dermatitis contact	0	2 (1.0)	0
* Table is limited to adverse reactions that occurred with higher incidence in PREGABALIN SUSTAINED RELEASE TABLET-treated patients than in placebo-treated patients for the DB Phase of the study.			

Other Adverse Reactions Observed During Clinical Studies with PREGABALIN and PREGABALIN SUSTAINED RELEASE TABLET

In addition to the adverse reactions reported during the controlled studies with PREGABALIN SUSTAINED RELEASE TABLET in postherpetic neuralgia, the following adverse reactions have been reported in patients treated with PREGABALIN and PREGABALIN SUSTAINED RELEASE TABLET during all clinical studies. This listing does not include those adverse reactions already listed above. The adverse reactions are categorized by system organ class and listed in order of decreasing frequency according to the following definitions: frequent adverse reactions are those occurring on 1 or more occasions in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; rare reactions are those occurring in fewer than 1/1000 patients.

Cardiac Disorders - *Infrequent:* Palpitations, Deep thrombophlebitis, Heart failure, Hypotension, Postural hypotension, Retinal vascular disorder, Syncope; *Rare:* Cardiac failure, Tachycardia

Eye Disorders - *Infrequent:* Periorbital edema

Gastrointestinal Disorders - *Frequent:* Increased appetite; *Infrequent:* Abdominal distension, Abdominal pain, Dysphagia, Pancreatitis, Tongue edema

General Disorders - *Frequent:* Fever; *Infrequent:* Chest pain, Face edema; *Rare:* Facial pain, Mucosal dryness

Hemic and Lymphatic System Disorders - *Frequent:* Ecchymosis; *Infrequent:* Anemia, Eosinophilia, Hypochromicanemia,Leukocytosis, Leukopenia, Lymphadenopathy, Thrombocytopenia; *Rare:* Myelofibro sis, Polycythemia, Prothrombin decreased, Purpura, Thrombocythemia

Infections and Infestations - *Infrequent:* Otitis media, Pneumonia

Investigations - *Rare:* Glucose urine present, Lipase increased, Neutrophil count increased, Proteinuria

Metabolic and Nutritional Disorders - *Rare:* Glucose Tolerance Decreased, Urate Crystalluria

Musculoskeletal and Connective Tissue Disorders - *Frequent:* Leg cramps, Myalgia, Myasthenia; *Infrequent:* Joint stiffness; *Rare:* Coccydynia, Myokymia

Nervous System Disorders - *Frequent:* Anxiety, Depersonalization, Hypertonia, Hypoesthesia, Libido decreased, Nystagmus, Paresthesia, Sedation, Stupor,

Twitching; *Infrequent:* Coordination abnormal, Abnormal dreams, Agitation, Amnesia, Apathy, Aphasia, Circumoral paresthesia, Cognitive disorder, Dysarthria, Dysgeusia, Hallucinations, Hostility, Hyperalgesia, Hyperesthesia, Hyperkinesia, Hypokinesia, Hypotonia, Libido increased, Myoclonus, Neuralgia, Sciatica, Sleep phase rhythm disturbance; *Rare:* Addiction, Altered state of consciousness, Bradykinesia, Cerebellar syndrome, Cogwheel rigidity, Coma, Delirium, Delusions, Depressed level of consciousness, Dysautonomia, Dyskinesia, Dystonia, Encephalopathy, Extrapyramidal syndrome, Psychomotor hyperactivity, Psychomotor skills impaired.

Psychiatric Disorders - *Infrequent:* Irritability

Respiratory System Disorders - *Rare:* Lung edema

Skin Disorders - *Frequent:* Pruritus; *Rare:* Stevens-Johnson syndrome

Special Senses - *Frequent:* Conjunctivitis, Tinnitus

Urogenital System Disorders - *Frequent:* Anorgasmia, Impotence, Urinary frequency, Urinary incontinence; *Infrequent:* Abnormal ejaculation, Albuminuria, Dysuria, Hematuria, Kidney calculus, Leukorrhea, Nephritis, Oliguria, Urinary retention

Post marketing Experience With PREGABALIN

The following adverse reactions have been identified during post-approval use of PREGABALIN. These adverse reactions have not been listed above and data are insufficient to support an estimate of their incidence or to establish causation. The listing is alphabetized: breast enlargement, gynecomastia.

There are also post marketing reports of respiratory failure and coma in patients taking pregabalin and other CNS depressant medications. In addition, 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.

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org/

4.9 Overdose

Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans

There is limited experience with overdose of pregabalin. The highest reported accidental overdose of PREGABALIN during the clinical development program was 8000 mg, and there were no notable clinical consequences.

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.

Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment. Standard hemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours).

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pregabalin binds with high affinity to the alpha2-delta site (an auxiliary subunit of voltage-gated calcium channels) in central nervous system tissues. Although the mechanism of action of pregabalin has not been fully elucidated, results with genetically modified mice and with compounds structurally related to pregabalin (such as gabapentin) suggest that binding to the alpha2-delta subunit may be involved in pregabalin's anti-nociceptive and antiseizure effects in animals. In animal models of nerve damage, pregabalin has been shown to reduce calcium-dependent release of pro-nociceptive neurotransmitters in the spinal cord, possibly by disrupting alpha2-delta containing-calcium channel trafficking and/or reducing calcium currents. Evidence from other animal models of nerve damage and persistent pain suggest the anti- nociceptive activities of pregabalin may also be mediated through interactions with descending noradrenergic and serotonergic pathways originating from the brainstem that modulate pain transmission in the spinal cord.

While pregabalin is a structural derivative of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), it does not bind directly to GABAA, GABAB, or benzodiazepine receptors, does not augment GABAA responses in cultured neurons, does not alter rat brain GABA concentration or have acute effects on GABA uptake or degradation. However, in cultured neurons prolonged application of pregabalin increases the density of GABA transporter protein and increases the rate of functional GABA transport. Pregabalin does not block sodium channels, is not active at opiate receptors, and does not alter cyclooxygenase enzyme activity. It is inactive at serotonin and dopamine receptors and does not inhibit dopamine, serotonin, or noradrenaline reuptake.

5.2 Pharmacokinetic properties

PREGABALIN SUSTAINED RELEASE TABLET has linear pharmacokinetics with dose-proportional increases in maximum plasma concentration (Cmax) and area under the plasma concentration-time curve (AUC) from 82.5-660 mg/day. Following repeated administration, steady state is achieved within approximately 48-72 hours.

PREGABALIN SUSTAINED RELEASE TABLET administered once daily following an evening meal has equivalent AUC and lower Cmax relative to a comparative dose of PREGABALIN administered without food twice daily (Table 5). Variability in Cmax and AUC for PREGABALIN SUSTAINED RELEASE TABLET is less than or equal to 25%.

Table 5: Steady-State Pharmacokinetics for PREGABALIN SUSTAINED RELEASE TABLET 165mg Once Daily and PREGABALIN 75 mg Twice Daily

	PREGABALIN SUSTAINED RELEASE TABLET Once Daily	**PREGABALIN BID**
N	24	24
Cmax (µg/mL)	2.0 (17)	3.2 (21)
Tmax (h)	8.0 (5.0 - 12.0)	0.7 (0.7 - 1.5)
AUC24 (µg•h/mL)	29.4 (17)	31.5 (18)
Cmin (µg/mL)	0.44 (24)	0.59 (25)

Note: Geometric mean (%CV) for AUC24, Cmax, Cmin; median (range) for Tmax.
Abbreviations: AUC24=area under the curve over 24 hours; BID=every 12 hours; Cmax=peak concentrations; Cmin=minimum concentrations; N=Number of subjects ; Tmax=time to peak concentrations.

Absorption

Pregabalin is absorbed from the small intestine and proximal colon. PREGABALIN SUSTAINED RELEASE TABLET absorption is linear and dose proportional.

The bioavailability of PREGABALIN SUSTAINED RELEASE TABLET is reduced if taken on an empty stomach. The AUC is approximately 30% lower when PREGABALIN SUSTAINED RELEASE TABLET is administered fasted relative to following an evening meal.

When PREGABALIN SUSTAINED RELEASE TABLET is administered following a 600 to 750 calorie (50% carbohydrates, 20% protein, 30% fat) evening meal, peak plasma concentrations occur within approximately 8 to 10 hours and AUC is approximately 93% to 97% relative to a comparative dose of PREGABALIN. The rate and extent of PREGABALIN SUSTAINED RELEASE TABLET absorption is similar when administered following a 400 to 500 calorie, 30% fat or an 800 to 1000 calorie, 15%, 30%, or 50% fat evening meal.

When PREGABALIN SUSTAINED RELEASE TABLET is administered following an 800 to 1000 calorie (50% carbohydrates, 20% protein, 30% fat) morning meal, peak plasma concentrations occur within approximately 12 hours and AUC is 99% relative to a comparative dose of PREGABALIN. AUC decreases approximately 13% to 25% when PREGABALIN SUSTAINED RELEASE TABLET is administered following a 400 to 500 calorie or 600 to 750 calorie (50% carbohydrates, 20% protein, 30% fat) morning meal relative to the 800 to 1000 calorie meal, while Cmax remains the same.

Distribution

Pregabalin does not bind to plasma proteins. The apparent volume of distribution of pregabalin following oral administration is approximately 0.5 L/kg. Pregabalin is a substrate for system L transporter which is responsible for the transport of large amino acids across the blood brain barrier. Although there are no data in humans, pregabalin has been shown to cross the blood brain barrier in mice, rats, and monkeys. In addition, pregabalin has been shown to cross the placenta in rats and is present in the milk of lactating rats.

Elimination

Metabolism

Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabeled pregabalin, approximately 90% of the administered dose was recovered in the urine as unchanged pregabalin. The N- methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0.9% of the dose. In preclinical studies, pregabalin (S-enantiomer) did not undergo racemization to the R- enantiomer in mice, rats, rabbits, or monkeys.

Excretion

Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug with a mean elimination half-life of 6.3 hours in subjects with normal renal function. Mean renal clearance was estimated to be 67.0 to 80.9 mL/min in young healthy subjects. Because pregabalin is not bound to plasma proteins this clearance rate indicates that renal tubular reabsorption is involved.

Pregabalin elimination is nearly proportional to CLcr.

Specific Populations

Age: Geriatric Patients

Pregabalin oral clearance tended to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with age-related decreases in CLcr. Reduction of pregabalin dose may be required in patients who have age-related compromised renal function.

Sex

Population pharmacokinetic analyses of the clinical studies showed that the relationship between daily dose and PREGABALIN SUSTAINED RELEASE TABLET drug exposure is similar between genders.

Race/Ethnicity

In population pharmacokinetic analyses of the clinical studies of PREGABALIN and PREGABALIN SUSTAINED RELEASE TABLET, the pharmacokinetics of pregabalin were not significantly affected by race (Caucasians, Blacks, and Hispanics).

Renal Impairment

Pregabalin clearance is nearly proportional to CLcr. Dosage reduction in patients with reduced renal function is necessary. Pregabalin is effectively removed from plasma by hemodialysis. Following a 4-hour hemodialysis treatment, plasma pregabalin concentrations are reduced by approximately 50%. For patients on hemodialysis, treatment with PREGABALIN SUSTAINED RELEASE TABLET is not recommended.

5.3 Preclinical safety data Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenesis

A dose-dependent increase in the incidence of malignant vascular tumors (hemangiosarcomas) was observed in 2 strains of mice (B6C3F1 and CD-1) given pregabalin (200, 1000, or 5000 mg/kg) in the diet for 2 years. Plasma pregabalin exposure (AUC) in mice receiving the lowest dose that increased hemangiosarcomas was approximately equal to the human exposure at the maximum recommended human dose (MRD) of 660 mg/day. A no-effect dose for induction of hemangiosarcomas in mice was not established. No evidence of carcinogenicity was seen in 2 studies in Wistar rats following dietary administration of pregabalin for 2 years at doses (50, 150, or 450 mg/kg in males and 100, 300, or 900 mg/kg in females) that were associated with plasma exposures in males and females up to approximately 15 and 26 times, respectively, human exposure at the MRD.

Mutagenesis

Pregabalin was not mutagenic in bacteria or in mammalian cells in vitro, was not clastogenic in mammalian systems in vitro and in vivo, and did not induce unscheduled DNA synthesis in mouse or rat hepatocytes.

Impairment Of Fertility

In fertility studies in which male rats were orally administered pregabalin (50 to

2500 mg/kg) prior to and during mating with untreated females, a number of adverse reproductive and developmental effects were observed. These included decreased sperm counts and sperm motility, increased sperm abnormalities, reduced fertility, increased preimplantation embryo loss, decreased litter size, decreased fetal body weights, and an increased incidence of fetal abnormalities. Effects on sperm and fertility parameters were reversible in studies of this duration (3–4 months). The no-effect dose for male reproductive toxicity in these studies (100 mg/kg) was associated with a plasma pregabalin exposure (AUC) approximately 4 times human exposure at the MRD of 660 mg/day.

In addition, adverse reactions on reproductive organ (testes, epididymides) histopathology were observed in male rats exposed to pregabalin (500 to 1250 mg/kg) in general toxicology studies of 4 weeks or greater duration. The no-effect dose for male reproductive organ histopathology in rats (250 mg/kg) was associated with a plasma exposure approximately 10 times human exposure at the MRD.

In a fertility study in which female rats were given pregabalin (500, 1250, or 2500 mg/kg) orally prior to and during mating and early gestation, disrupted estrous cyclicity and an increased number of days to mating were seen at all doses, and embryo lethality occurred at the highest dose. The low dose in this study produced a plasma exposure approximately 10 times that in humans receiving the MRD. A no-effect dose for female reproductive toxicity in rats was not established.

6. Pharmaceutical particulars

6.1 List of excipients Tablet core

Hydroxy Propyl Methyl Cellulose (HPMC-K-100)
Polyvinyl Pyrrolidone (PVPK-30)
Microcrystalline Cellulose 112
Purified Talc
Magnesium Stearate
Colloidal anhydrous Silica
Iso Propyl alcohol

Film-coat

Hydroxy propyl methyl cellulose (E 15)
Purified Talcum
Iso Propyl alcohol
Methylene Dichloride Erythrosine
Polyethylene glycol (PEG-6000)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at a temperature not exceeding 30°C. Protect from light.

6.5 Nature and contents of container

10 tablets are packed in an Alu - Alu blister and 3 such blisters are packed in a carton along with package insert.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with localrequirements.

7. Marketing authorization holder and manufacturing sites

Marketing authorization holder:

Company Name:	Galaxy pharmaceutical ltd.
Address:	1st Floor, Doctors Park, 3rd Parkland Avenue, P.O.BOX 39107 - 00623,
Country:	Nairobi (Kenya).

Manufacturing site address:

Company Name:	Saitech Medicare pvt. Ltd.
Address:	Trilokpur road, kala-amb Dist. Sirmor, himachal pradesh
Country:	India

8. Marketing authorization number

H2024/CTD9276/21332

9. Date of first registration

13/02/2024

10. Date of revision of the text

November 2024