SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Pregabalin 82.5 mg film-coated tablets
Epibalin ER 82.5

Pregabalin 165 mg film-coated tablets
Epibalin ER 165

2. Qualitative and quantitative composition

Epibalin ER 82.5
Each tablet contains 82.5 mg of pregabalin.

Epibalin ER 165
Each tablet contains 165 mg of pregabalin.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Tablet.

Epibalin ER 82.5
Brown-coloured, almond-shaped, biconvex film-coated tablets debossed with “MP 12” on one side and plain on the other side.

Epibalin ER 165
Pink-coloured, almond-shaped, biconvex film-coated tablets debossed with “MP 11” on one side and plain on the other side.

4. Clinical particulars

4.1 Therapeutic indications

Pregabalin is indicated for the management of
- Neuropathic pain associated with diabetic peripheral neuropathy.
- Postherpetic neuralgia.

The efficacy of pregabalin 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

4.2.1 Important dosage and administration instructions

Epibalin should be administered once daily after an evening meal. Epibalin should be swallowed whole and should not be split, crushed, or chewed.

When discontinuing Epibalin, taper gradually over a minimum of 1 week. Instruct patients that if they miss taking their dose of Epibalin after an evening meal, then they should take their usual dose of Epibalin before bedtime following a snack. If they miss taking the dose of Epibalin before bedtime, then they should take their usual dose of Epibalin following a morning meal. If they miss taking the dose of Epibalin following the morning meal, then they should take their usual dose of Epibalin at the usual time that evening following an evening meal.

4.2.2 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 is 330 mg once daily.

Although pregabalin use was studied at 600 mg/day, there was no evidence that this dose conferred additional significant benefit and this dose was less well tolerated. Given the dose-dependent adverse reactions with pregabalin, treatment with doses above 330 mg/day is not recommended for Epibalin.

4.2.3 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 can tolerate pregabalin, may be treated with up to 660 mg once daily. Given 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 ongoing pain and are tolerating 330 mg daily. The maximum recommended dose of pregabalin is 660 mg once daily.

4.2.4 Conversion from pregabalin capsules or oral solution to Epibalin

When switching from pregabalin capsules to Epibalin, on the day of the switch, instruct patients to take their morning dose of pregabalin capsules as prescribed and initiate Epibalin therapy after an evening meal.

Table 1. Conversion from pregabalin capsules or oral solution to Epibalin

Pregabalin capsules total daily dose (dosed 2 or 3 times daily)	Epibalin 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 × 82.5 mg tablets taken once a day.
b. 495 mg = 3 × 165 mg tablets taken once a day.
c. 660 mg = 2 × 330 mg tablets taken once a day.

4.2.5 Patients with renal impairment

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

Given 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:

$$CLCr = \frac{[140 - \text{age (years)}] \times \text{weight (Kg)}}{72 \times \text{serum creatinine (mg/ dL)}} \quad (\times 0.85 \text{ for female patients})$$

Next, refer to the Dosage and Administration section to determine the recommended total daily dose based on indication, for a patient with normal renal function (CLcr greater than or equal to 60 mL/min). Then refer to Table 2 to determine the corresponding renal adjusted dose. (For example: A patient initiating pregabalin therapy for postherpetic neuralgia with normal renal function [CLcr greater than or equal to 60 mL/min], receives a single daily dose of 165 mg/day Epibalin. Therefore, a renal impaired patient with a CLcr of 50 mL/min would receive a single daily dose of 82.5 mg.)

Table 2. Epibalin dosage adjustment based on renal function

Creatinine clearance (CLcr) (mL/min)	**Total Epibalin daily dose (mg/day)**				**Dose Regimen**
greater than or equal to 60	165	330	495a	660b	Once a day
30–60	82.5	165	247.5c	330	Once a day
less than 30/hemodialysis	Dose with pregabalin capsules				

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

4.3 Contraindications

Epibalin 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 [see Warnings and Precautions (4.4.1, 4.4.2), Adverse Reactions (4.8)].

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 capsules. 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 Epibalin immediately in patients with these symptoms.

Exercise caution when prescribing Epibalin 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 reactions

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

4.4.3 Suicidal behaviour and ideation

Antiepileptic drugs (AEDs), including pregabalin, the active ingredient in Epibalin, increase the risk of suicidal thoughts or behaviour in patients taking these drugs for any indication. Monitor patients treated with any AED for any indication of the emergence or worsening of depression, suicidal thoughts or behaviour, and/or any unusual changes in mood or behaviour.

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 behaviour compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behaviour 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 behaviour 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 the drug's effect on suicide.

The increased risk of suicidal thoughts or behaviour 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 behaviour beyond 24 weeks could not be assessed.

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

Anyone considering prescribing Epibalin must balance the risk of suicidal thoughts or behaviour with the risk of untreated illness. Many other illnesses for which AEDs are prescribed are associated with morbidity and mortality and an increased risk of suicidal thoughts and behaviour. Should suicidal thoughts and behaviour 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 can increase the risk of suicidal thoughts and behaviour 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 behaviour, or the emergence of suicidal thoughts, behaviour, or thoughts about self-harm. Report behaviours of concern immediately to healthcare providers.

4.4.1 Peripheral oedema

Pregabalin treatment may cause peripheral oedema. In short-term trials of patients without clinically significant heart or peripheral vascular disease, there was no apparent association between peripheral oedema and cardiovascular complications such as hypertension or congestive heart failure. Peripheral oedema 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 oedema for patients receiving pregabalin in the single-blind phase was 5.3 % of patients. In controlled clinical trials for pain indications, 0.8 % of pregabalin patients withdrew due to peripheral oedema during the single-blind phase.

Higher frequencies of weight gain and peripheral oedema were observed in patients taking both pregabalin capsules 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 oedema 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 capsules only, and 19 % (23/120) of patients who were on both pregabalin capsules 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 capsules 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 oedema when co-administering Epibalin and these agents. There is limited data on congestive heart failure patients with New York Heart Association (NYHA) Class III or IV cardiac status, therefore, patients should be monitored for possible exacerbation of congestive heart failure symptoms when using Epibalin.

4.4.1 Dizziness and somnolence
Pregabalin may cause dizziness and somnolence. Inform patients that Epibalin-related dizziness and somnolence may impair their ability to perform tasks such as driving or operating machinery. Concomitant use of pregabalin with other central nervous system (CNS) depressants may exacerbate these effects [see Drug Interactions (4.5)].

In the pregabalin-controlled trials for pain indications, dizziness was experienced by 24 % of pregabalin-treated patients during the single-blind phase; somnolence was experienced by 15.8 % of Epibalin-treated patients. Dizziness and somnolence generally began shortly after the initiation of Epibalin 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 capsules-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.

4.4.2 Weight gain
Pregabalin treatment may cause weight gain. In Epibalin-controlled trials for pain indications, weight gain was experienced by 4 % of Epibalin-treated patients during the single-blind phase. Adverse events of weight gain were observed in 3.7 % of Epibalin-treated patients and 1% of placebo-treated patients during the double-blind phase.

In pregabalin capsules controlled clinical trials of up to 14 weeks, a gain of 7 % or more over baseline weight was observed in 9 % of pregabalin capsules-treated patients and 2 % of placebo-treated patients. Few patients treated with pregabalin capsules (0.3 %) withdrew from controlled trials due to weight gain. In studies with pregabalin capsules, 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 oedema [see Warnings and Precautions (4.4.4)]. Although weight gain was not associated with clinically important changes in blood pressure in short-term controlled studies with pregabalin capsules, the long-term cardiovascular effects of pregabalin-associated weight gain are unknown.

Among diabetic patients, pregabalin capsules-treated patients gained an average of 1.6 kg (range: -16 to 16 kg), compared to an average 0of .3 kg (range: -10 to 9 kg) weight gain in placebo patients. In a cohort of 333 diabetic patients who received pregabalin capsules for at least 2 years, the average weight gain was 5.2 kg. While the effects of Epibalin-associated weight gain on glycemic control have not been systematically assessed, in controlled and longer-term open-label clinical trials with diabetic patients, pregabalin capsules treatment did not appear to be associated with loss of glycemic control (as measured by HbA1C).

4.4.4 Risks associated with abrupt or rapid discontinuation
Following abrupt or rapid discontinuation of Epibalin, some patients reported symptoms including insomnia, nausea, headache, anxiety, and diarrhoea Increased seizure frequency

may occur in patients with seizure disorders taking pregabalin for pain if Epibalin is rapidly discontinued. Taper Epibalin gradually over a minimum of 1 week rather than discontinuing the drug abruptly. The efficacy of pregabalin as adjunctive therapy for adult patients with partial-onset seizures has not been established.

4.4.5 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 [see Nonclinical Toxicology (5.3.1)]. The clinical significance of this finding is unknown. Clinical experience during the remarketing development of pregabalin capsules provides no direct means to assess its potential for inducing tumours 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 pre-existing tumours 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.

4.4.6 Ophthalmological effects

In controlled studies for pain indications, 4.8 % of patients treated with Epibalin in the single-blind phase reported blurred vision, which resolved in a majority of cases with continued dosing. Less than 1 % of patients discontinued Epibalin treatment due to vision-related events (primarily blurred vision). Additionally, 0.7 % of Epibalin-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 capsules-treated patients and 5 % of placebo-treated patients. Visual field changes were detected in 13 % of pregabalin capsules-treated and 12 % of placebo-treated patients. Funduscopic changes were observed in 2 % of pregabalin capsules-treated and 2 % of placebo-treated patients.

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

4.4.7 Creatine kinase elevations

Pregabalin capsules treatment was associated with creatine kinase elevations. Mean changes in creatine kinase from baseline to the maximum value were 60 U/L for pregabalin capsules-treated patients and 28 U/L for the placebo patients. In all controlled trials across multiple patient populations, 1.5 % of patients on pregabalin capsules and 0.7 % of placebo patients had a value of creatine kinase at least 3 times the upper limit of normal. Three pregabalin capsules-treated subjects had events reported as rhabdomyolysis in premarketing clinical trials. The relationship between these myopathy events and pregabalin capsules 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 Epibalin if myopathy is diagnosed or suspected or if markedly elevated creatine kinase levels occur.

4.4.8 Decreased platelet count

Both Epibalin and pregabalin capsules treatment were associated with a decrease in platelet count. In the double-blind phase of controlled studies for pain indication, Epibalin-treated patients experienced a median change from baseline in platelet count of 11 × 103/mm^3 (for the PHN population) and 14 × 103/mm^3 (for the FM population) as compared to 1 × 103/mm3 in placebo-treated patients (for both populations). Pregabalin capsules-treated patients experienced a mean maximal decrease in platelet count of 20 × 103/µL, compared to 11 × 103/µL in placebo patients. In the overall database of controlled trials, 2 % of placebo patients and 3 % of pregabalin capsules patients experienced a potentially clinically significant decrease in platelets, defined as 20 % below baseline value and less than 150 × 103/µL. A single pregabalin capsules-treated subject developed severe thrombocytopenia with a platelet count less than 20 × 103/µL. In randomized controlled trials, pregabalin capsules or Epibalin were not associated with an increase in bleeding-related adverse reactions.

4.4.9 PR interval prolongation

Pregabalin capsules 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 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 patients taking other PR-prolonging medications. However, these analyses cannot be considered definitive because of the limited number of patients in these categories.

4.5 Interaction with other medicinal products and other forms of interaction

Since pregabalin is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (less than 2% of a dose recovered in urine as metabolites), and does not bind to plasma proteins, its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions or protein binding displacement. In vitro studies showed that pregabalin is unlikely to be involved in significant pharmacokinetic drug interactions [see Clinical Pharmacology (5)].

The interactions of Epibalin with co-administration of other drugs have not been systematically evaluated. Co-administration of the prokinetic drug erythromycin with Epibalin did not result in any clinically important changes in the pharmacokinetics of pregabalin [see Clinical Pharmacology (12)]. Additional studies have been performed with pregabalin capsules. No pharmacokinetic interactions were observed between pregabalin capsules and carbamazepine, gabapentin, lamotrigine, oral contraceptives, phenobarbital, phenytoin, topiramate, and valproic acid. A similar lack of pharmacokinetic interactions would be expected to occur with Epibalin.

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

4.6 Fertility, pregnancy and lactation

4.6.1 Pregnancy

Risk Summary
There are no adequate and well-controlled studies with Pregabalin 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 [see Data]. 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 is unknown. However, the background risk in the U.S. general population of major birth defects is 2-4% and miscarriage is 15-20% of clinically recognized pregnancies. Advise pregnant women of the potential risk to a fetus.

Data

Animal data
When pregnant rats were given pregabalin (500, 1250, or 2500 mg/kg) orally throughout the period of organogenesis, incidences of specific skull alterations attributed to abnormally advanced ossification (premature fusion of the jugal and nasal sutures) were increased at greater than or equal to 1250 mg/kg, and incidences of skeletal variations and retarded ossification were increased at all doses. Fetal body weights were decreased at the highest dose. The low dose in this study was associated with plasma exposure (AUC) approximately 18 times human exposure at the MRD of 660 mg/day. A no-effect dose for rat embryo-fetal developmental toxicity was not established. When pregnant rabbits were given pregabalin (250, 500, or 1250 mg/kg) orally throughout the period of organogenesis, decreased fetal body weight and increased incidences of skeletal malformations, visceral variations, and retarded ossification were observed at the highest dose. The no-effect dose for developmental toxicity in rabbits (500 mg/kg) was associated with plasma exposure approximately 17 times human exposure at the MRD.

In a study in which female rats were dosed with pregabalin (50, 100, 250, 1250, or 2500 mg/kg) throughout gestation and lactation, offspring growth was reduced at greater than or equal to 100 mg/kg and offspring survival was decreased at greater than or equal to 250 mg/kg. The effect on offspring survival was pronounced at doses greater than or equal to 1250 mg/kg, with 100 % mortality in high-dose litters. When offspring were tested as adults, neurobehavioral abnormalities (decreased auditory startle responding) were observed at greater than or equal to 250 mg/kg and reproductive impairment (decreased fertility and litter

size) was seen at 1250 mg/kg. The no-effect dose for pre-and postnatal developmental toxicity in rats (50 mg/kg) produced a plasma exposure approximately 2 times human exposure at the MRD. In the prenatal-postnatal study in rats, pregabalin prolonged gestation and induced dystocia at exposures greater than or equal to 50 times the mean human exposure (AUC(0–24) of 123 µg·hr/mL) at the MRD.

4.6.2 Lactation

Risk Summary
Small amounts of pregabalin have been detected in the milk of lactating women. A pharmacokinetic study in lactating women detected pregabalin in breast milk at 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 [see Data]. The study did not evaluate the effects of pregabalin on milk production or the effects of pregabalin on the breastfed infant.

Based on animal studies, there is a potential risk of tumorigenicity with pregabalin exposure via breast milk to the breastfed infant [see Nonclinical Toxicology (5.3.1)]. Available clinical study data in patients greater than 12 years of age do not provide a clear conclusion about the potential risk of tumorigenicity with pregabalin [see Warnings and Precautions (4.4.8)]. Because of the potential risk of tumorigenicity, breastfeeding is not recommended during treatment with Pregabalin.

Data
A pharmacokinetic study in ten lactating women, who were at least 12 weeks postpartum, evaluated the concentrations of pregabalin in plasma and breast milk. Pregabalin capsules 150 mg oral capsule was given every 12 hours (300 mg daily dose) for a total of 4 doses. Pregabalin was detected in breast milk at 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. The study did not evaluate the effects of pregabalin on milk production. Infants did not receive breast milk obtained during the dosing period, therefore, the effects of pregabalin on the breastfed infant were not evaluated.

4.6.3 Females and males of reproductive potential

Infertility

Males
Effects on spermatogenesis
In a randomized, double-blind, placebo-controlled non-inferiority study to assess the effect of pregabalin on sperm characteristics, healthy male subjects received pregabalin at a daily dose of up to 600 mg (n=111) or placebo (n=109) for 13 weeks (1 complete sperm cycle) followed by a 13-week washout period (off-drug). A total of 65 subjects in the pregabalin group (59 %) and 62 subjects in the placebo group (57 %) were included in the per-protocol (PP) population. These subjects took the study drug for at least 8 weeks, had appropriate timing of semen collections and did not have any significant protocol violations. Among these subjects, approximately 9% of the pregabalin group (6/65) vs. 3 % in the placebo group (2/62) had

greater than or equal to a 50 % reduction in mean sperm concentrations from baseline at Week 26 (the primary endpoint). The difference between pregabalin and placebo was within the pre-specified non-inferiority margin of 20%. There were no adverse effects of pregabalin on sperm morphology, sperm motility, serum FSH or serum testosterone levels as compared to placebo. In subjects in the PP population with greater than or equal to 50 % reduction in sperm concentration from baseline, sperm concentrations were no longer reduced by greater than or equal to 50% in any affected subject after an additional 3 months off-drug. In 1 subject, however, subsequent semen analyses demonstrated reductions from baseline of greater than or equal to 50 % at 9 and 12 months off-drug. The clinical relevance of these data is unknown. In the animal fertility study with pregabalin in male rats, adverse reproductive and developmental effects were observed [see Nonclinical Toxicology (5.3.1)].

4.6.4 Pediatric use

The safety and effectiveness of Pregabalin in pediatric patients have not been established.

Juvenile animal toxicity data

In studies in which pregabalin (50 to 500 mg/kg) was orally administered to young rats from early in the postnatal period (Postnatal Day 7) through sexual maturity, neurobehavioral abnormalities (deficits in learning and memory, altered locomotor activity, decreased auditory startle responding and habituation) and reproductive impairment (delayed sexual maturation and decreased fertility in males and females) were observed at doses greater than or equal to 50 mg/kg. The neurobehavioral changes of acoustic startle persisted at greater than or equal to 250 mg/kg and locomotor activity and water maze performance at greater than or equal to 500 mg/kg in animals tested after cessation of dosing and, thus, were considered to represent long-term effects. The low effect dose for developmental neurotoxicity and reproductive impairment in juvenile rats (50 mg/kg) was associated with plasma pregabalin exposure (AUC) approximately equal to human exposure at the maximum recommended dose of 660 mg/day. A no-effect dose was not established.

4.6.5 Geriatric use

In controlled clinical studies of pregabalin capsules in neuropathic pain associated with diabetic peripheral neuropathy, 246 patients were 65 to 74 years of age, and 73 patients were 75 years of age or older. In controlled clinical studies of pregabalin capsules in neuropathic pain associated with postherpetic neuralgia, 282 patients were 65 to 74 years of age, and 379 patients were 75 years of age or older. In the Epibalin neuropathic pain associated with postherpetic neuralgia study, 422 patients 65 years of age and older received Epibalin.

No overall differences in safety and effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Pregabalin is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. See Dosage and Administration (4.2.5) for recommendations for dosing in patients with renal impairment.

4.7 Effects on the ability to drive and use machines

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. Concomitant use of Pregabalin with other central nervous system (CNS) depressants may exacerbate these effects [see Drug Interactions (4.5)].

4.8 Undesirable effects

The following adverse reactions are described elsewhere in the labelling:

- Angioedema [see Warnings and Precautions (4.4.1)]
- Hypersensitivity Reactions [see Warnings and Precautions (4.4.2)]
- Suicidal Behavior and Ideation ([see Warnings and Precautions (4.4.3)]
- Peripheral Oedema [see Warnings and Precautions (4.4.4)]
- Dizziness and Somnolence [see Warnings and Precautions (4.4.5)]
- Weight Gain [see Warnings and Precautions (4.4.6)]
- Ophthalmological Effects [see Warnings and Precautions (4.4.9)]
- Creatine Kinase Elevations [see Warnings and Precautions (4.4.10)]
- Decreased Platelet Count [see Warnings and Precautions (4.4.11)]

4.8.1 Clinical Trials Experience

Clinical trials are conducted under widely varying conditions, therefore, 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. 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 oedema, 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 oedema, nausea, blurred vision, dry mouth, and weight gain.

<u>Controlled study in postherpetic neuralgia</u>

Adverse reactions leading to discontinuation

In a clinical trial in patients with postherpetic neuralgia, 8.9% of patients treated with Pregabalin 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 oedema (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, 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 study in patients with postherpetic neuralgia*

System Organ Class Preferred Term	**Single-Blind Phase**	**Double-Blind Phase**	
	Pregabalin [N=801] n (%)	**Pregabalin [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)	0
Vomiting	9 (1.1)	3 (1.4)	1 (0.5)
General disorders and administration site conditions			
Oedema peripheral	39 (4.9)	8 (3.8)	1 (0.5)
Fatigue	31 (3.9)	3 (1.4)	2 (1.0)
Oedema	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 (1.4)	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

The table is limited to adverse reactions that occurred with a higher incidence in Epibalin-treated patients than in placebo-treated patients for the DB phase of the study.

Other adverse reactions observed during clinical studies with pregabalin capsules and Epibalin

In addition to the adverse reactions reported during the controlled studies with pregabalin in postherpetic neuralgia, the following adverse reactions have been reported in patients treated with pregabalin capsules and Epibalin 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. Adverse reactions of major clinical importance are described in the *Warnings and Precautions* section (4.4).

Cardiac disorders – *Infrequent*: Palpitations, deep thrombophlebitis, heart failure, hypotension, postural hypotension, retinal vascular disorder, syncope; *Rare*: Cardiac failure, tachycardia.
Eye disorders – *Infrequent*: Periorbital oedema
Gastrointestinal disorders – *Frequent*: Increased appetite; *Infrequent*: Abdominal distension, abdominal pain, dysphagia, pancreatitis, tongue oedema.
General disorders – *Frequent*: Fever; *Infrequent*: Chest pain, face oedema; *Rare*: Facial pain, mucosal dryness.

Hemic and lymphatic system disorders – *Frequent*: Ecchymosis; *Infrequent*: Anemia, eosinophilia, hypochromic anaemia, leukocytosis, leukopenia, lymphadenopathy, thrombocytopenia; *Rare*: Myelofibrosis, 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 oedema
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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It
allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the e-PV desktop applications
(https://drive.google.com/file/d/16hwTz0587ZWtSWadbBAMwQPOD_KSExZP/view) or search for e-PV Mobile applications on the Google Play or Apple App Store.

4.9 Overdose

Signs, symptoms and laboratory findings of acute overdosage in humans
There is limited experience with an overdose of pregabalin. The highest reported accidental overdose of pregabalin capsules 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

Pharmacological classification: 13.1 Anticonvulsants.

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 suggests 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 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, a steady state is achieved within approximately 48-72 hours.

Pregabalin administered once daily following an evening meal has an equivalent AUC and lower Cmax relative to a comparative dose of pregabalin capsules administered without food twice daily (Table 5). The variability in C_{max} and AUC for pregabalin is less than or equal to 25 %.

Table 5. Steady-state pharmacokinetics for Epibalin 165 mg once daily and pregabalin capsules 75 mg twice daily

	Epibalin Once Daily	**Pregabalin capsules BID**
N	24	24

C_{max} (µg/mL)	2.0 (17)	3.2 (21)
T_{max} (h)	8.0 (5.0 – 12.0)	0.7 (0.7 – 1.5)
AUC_{24} (µg•h/mL)	29.4 (17)	31.5 (18)
C_{min} (µg/mL)	0.44 (24)	0.59 (25)

Note: Geometric mean (%CV) for AUC24, Cmax, Cmin; median (range) for Tmax.
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 absorption is linear and dose-proportional. The bioavailability of pregabalin is reduced if taken on an empty stomach. The AUC is approximately 30% lower when pregabalin is administered fasted relative to following an evening meal.

When pregabalin 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 capsules. The rate and extent of pregabalin 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 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 capsules. AUC decreases approximately 13 % to 25 % when Pregabalin 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 C_{max} 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 the system L transporter which is responsible for the transport of large amino acids across the blood-brain barrier. Although there is no data on 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 an 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 [see Dosage and Administration (4.2.5)].

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 [see Dosage and Administration (4.2.5)].

Sex
Population pharmacokinetic analyses of the clinical studies showed that the relationship between daily dose and Pregabalin drug exposure is similar between genders.

Race/Ethnicity
In population pharmacokinetic analyses of the clinical studies of pregabalin capsules and Pregabalin, 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 the plasma by hemodialysis. Following a 4-hour hemodialysis treatment, plasma pregabalin concentrations are reduced by approximately 50%. For patients on hemodialysis, treatment with Pregabalin is not recommended [see Dosage and Administration (4.2.5)].

Drug Interaction Studies

In vitro Studies
In vitro studies showed that pregabalin is unlikely to be involved in significant pharmacokinetic drug interactions. Pregabalin, at concentrations that were, in general, 10 times those attained in clinical trials, does not inhibit human CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 enzyme systems. *In vitro*, drug interaction studies demonstrate that pregabalin does not induce CYP1A2 or CYP3A activity. Therefore, an increase in the metabolism of co-administered CYP1A2 substrates (e.g., theophylline, caffeine) or CYP3A4 substrates (e.g., midazolam, testosterone) is not anticipated.

In vivo Studies
With the exception of erythromycin, the interactions of pregabalin with co-administration of other drugs have not been systematically evaluated. Additional studies have been performed with pregabalin capsules [see Drug Interactions (4.5)]. No pharmacokinetic interactions were observed between pregabalin capsules and carbamazepine, ethanol, gabapentin, lamotrigine, lorazepam, oral contraceptive, oxycodone, phenobarbital, phenytoin, topiramate, and valproic acid. A similar lack of pharmacokinetic interactions would be expected to occur with Epibalin.

The drug interaction studies described in this section were conducted in healthy adults and across various patient populations.

Erythromycin
Multiple-dose administration of erythromycin (500 mg every 6 hours for 18 hours) in healthy subjects resulted in a 17 % decrease in the AUC of Epibalin (330 mg single dose).

Ethanol
Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects did not affect the rate and extent of ethanol single-dose pharmacokinetics and single-dose administration of ethanol (0.7 g/kg) did not affect the steady-state pharmacokinetics of pregabalin. Additive effects on cognitive and gross motor functioning were seen when pregabalin capsules were co-administered with ethanol. No clinically important effects on respiration were seen [see Drug Interactions (4.5)].

Gabapentin
The pharmacokinetic interactions of pregabalin and gabapentin were investigated in 12 healthy subjects following concomitant single-dose administration of 100 mg pregabalin and 300 mg gabapentin and in 18 healthy subjects following concomitant multiple-dose administration of 200 mg pregabalin every 8 hours and 400 mg gabapentin every 8 hours. Gabapentin pharmacokinetics following single- and multiple-dose administration were unaltered by pregabalin co-administration. The extent of pregabalin absorption was unaffected by gabapentin co-administration, although there was a small reduction in the rate of absorption.

Lorazepam
Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects did not affect the rate and extent of lorazepam single-dose pharmacokinetics and single-dose administration of lorazepam (1 mg) did not affect the steady-state pharmacokinetics of pregabalin. Additive effects on cognitive and gross motor functioning were seen when pregabalin capsules were co-administered with lorazepam. No clinically important effects on respiration were seen [see Drug Interactions (4.5)].

Oral contraceptive
Pregabalin co-administration (200 mg 3 times a did not affect the steady-state pharmacokinetics of norethindrone and ethinyl estradiol (1 mg/35 µg, respectively) in healthy subjects.

Oxycodone
Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects did not affect the rate and extent of oxycodone single-dose pharmacokinetics. Single-dose administration of oxycodone (10 did not affect the steady-state pharmacokinetics of pregabalin. Additive effects on cognitive and gross motor functioning were seen when pregabalin capsules were co-administered with oxycodone. No clinically important effects on respiration were seen [see Drug Interactions (4.52)].

Carbamazepine, lamotrigine, phenobarbital, phenytoin, topiramate and valproic acid.

Steady-state trough plasma concentrations of phenytoin, carbamazepine, carbamazepine 10,11 epoxide, valproic acid, and lamotrigine were not affected by concomitant pregabalin (200 mg 3 times a day) administration.

Population pharmacokinetic analyses in patients treated with pregabalin and various concomitant medications suggest the following:

Therapeutic class	Specific concomitant drugs studied
Concomitant drug does not affect the pharmacokinetics of pregabalin	
Hypoglycemics	Glyburide, insulin, metformiN
Diuretics	Furosemide
Antiepileptic Drugs	Tiagabine
The concomitant drug does not affect the pharmacokinetics of pregabalin and pregabalin does not affect the pharmacokinetics of the concomitant drug	
Antiepileptic Drugs	Carbamazepine, lamotrigine, phenobarbital, phenytoin, topiramate, valproic acid

5.3 Preclinical safety data

5.3.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
A dose-dependent increase in the incidence of malignant vascular tumours (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 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) before and during mating with untreated females, several 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 plasma pregabalin exposure (AUC) approximately 4 times human exposure at the MRD of 660 mg/day.

In addition, adverse reactions on reproductive organ (testes and 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 before and during mating and early gestation, disrupted oestrous 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.

5.3.2 Animal Toxicology and/or Pharmacology

Dermatopathy
Skin lesions ranging from erythema to necrosis were seen in repeated-dose toxicology studies in both rats and monkeys. The aetiology of these skin lesions is unknown. At the MRD of 660 mg/day, there is a 2-fold safety margin for the dermatological lesions. The more severe dermatopathies involving necrosis were associated with pregabalin exposures (as expressed by plasma AUCs) of approximately 3 to 8 times those achieved in humans given the MRD. No increase in the incidence of skin lesions was observed in clinical studies.

Ocular lesions
Ocular lesions (characterized by retinal atrophy [including loss of photoreceptor cells] and/or corneal inflammation/mineralization) were observed in 2 lifetime carcinogenicity studies in Wistar rats. These findings were observed at plasma pregabalin exposures (AUC) greater than or equal to 2 times those achieved in humans given the maximum recommended dose of 660 mg/day. A no-effect dose for ocular lesions was not established. Similar lesions were not observed in lifetime carcinogenicity studies in 2 strains of mice or monkeys treated for 1 year.

6. Pharmaceutical particulars

6.1 List of excipients

Tablet core
Hypromellose
Microcrystalline cellulose PH 200
Croscarmellose sodium
Sodium lauryl sulphate
Syloid 244
Carbopol 71G
Magnesium stearate
Purified water

Tablet coat
Epibalin ER 82.5

Opadry® II Purple 85F500030

Epibalin ER 165
Opadry® II Pink 85F540289

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Store below 30°C.

6.5 Nature and contents of the container
The capsules are packed in aluminium blister packs.

Blister pack sizes of 1 x 10 tablets, 3 x 10 tablets and 10 x 10 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. APPLICANT
Msn Laboratories Private Limited
Formulations Division, Unit-II, Sy. No. 1277, 1319 to 1324, Nandigama (Village & Mandal)
Rangareddy District - 509 228
Telangana
India

8. MANUFACTURER
Msn Laboratories Private Limited
Formulations Division, Unit-II, Sy. No. 1277, 1319 to 1324, Nandigama (Village & Mandal)
Rangareddy District - 509 228
Telangana
India

9. REGISTRATION DETAILS
Epibalin ER 82.5
Zimbabwe registration number: 2023/13.1/6417
Zimbabwe category for distribution: Prescription Preparations Tenth Schedule (P.P.10)

Epibalin ER 165
Zimbabwe registration number: 2023/13.1/6418
Zimbabwe category for distribution: Prescription Preparations Tenth Schedule (P.P.10)

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