AUSTRALIAN PRODUCT INFORMATION
Pregablin Apotex, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg & 300 mg capsules

1. NAME OF THE MEDICINE

Pregabalin

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pregabalin is an analogue of the neurotransmitter gamma-aminobutyric acid (GABA). It has analgesic and anticonvulsant activity.

Pregablin Apotex capsules contain the active ingredient pregabalin.

Pregabalin is a white to off-white solid. It is sparingly soluble in water and basic and acidic aqueous solutions.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

PREGABLIN APOTEX 25 mg capsules:
Size: 4 Hard gelatin capsule, cap: light grey, body: light grey with “25” printed in black ink

PREGABLIN APOTEX 50 mg capsules*:
Size: 3 Hard gelatin capsule, cap: light grey, body: light grey with “50” and a black line printed in black ink

PREGABLIN APOTEX 75 mg capsules:
Size: 4 Hard gelatin capsule, cap: light red, body: light grey with “75” printed in black ink

PREGABLIN APOTEX 100 mg capsules*:
Size: 3 Hard gelatin capsule, cap: red, body: red with “100” printed in black ink

PREGABLIN APOTEX 150 mg capsules:
Size: 2 Hard gelatin capsule, cap: light grey, body: light grey with “150” printed in black ink

PREGABLIN APOTEX 200 mg capsules*:
Size: 1 Hard gelatin capsule, cap: red, body: red with “200” printed in black ink

PREGABLIN APOTEX 225 mg capsules*:
Size: 1 Hard gelatin capsule, cap: red, body: light grey with “225” printed in black ink

PREGABLIN APOTEX 300 mg capsules:
Size: 0 Hard gelatin capsule, cap: red, body: light grey with “300” printed in black ink

*non-marketed presentations

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

PREGABLIN APOTEX is indicated for the treatment of neuropathic pain in adults.

PREGABLIN APOTEX is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.

4.2. DOSE AND METHOD OF ADMINISTRATION

The dose range is 150 to 600 mg per day given in two divided doses.

Pregablin Apotex capsules may be taken with or without food.

Neuropathic Pain

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

Since diabetes is frequently complicated by renal disease, patients with diabetic neuropathy, in accordance with current clinical practice, should be assessed for renal impairment prior to commencing pregabalin and dosage adjusted appropriately.

The effectiveness of Pregabalin in the treatment of neuropathic pain has not been assessed in controlled clinical trials for treatment periods longer than 12 weeks (see CLINICAL TRIALS). The risks and benefits of treatment to an individual patient should be assessed before extending therapy for longer than 12 weeks.

Epilepsy

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

It is not necessary to monitor plasma pregabalin concentrations to optimise pregabalin therapy. Pregabalin does not alter the plasma concentrations of other commonly used anti-convulsant drugs. Similarly, commonly used anti-convulsant drugs do not alter plasma concentrations of pregabalin see Section 4.4 SPECIAL WARNING AND PRECAUTIONS FOR USE, Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

Discontinuation of Pregabalin

In accordance with current clinical practice, if pregabalin has to be discontinued, it is recommended to withdraw it gradually over a minimum of one week.

Use in Renal Impairment

Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. As pregabalin clearance is directly proportional to creatinine clearance see Section 5.2 PHARMACOKINETIC PROPERTIES, Excretion, dosage reduction in patients with compromised renal function must be individualised according to creatinine clearance (CLcr), as indicated in Table 1 determined using the following formula:

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

Pregabalin is removed effectively from plasma by haemodialysis (50% of drug in 4 hours). For patients receiving haemodialysis, the pregabalin daily dose should be adjusted based on renal function. In addition to the daily dose, a supplementary dose should be given immediately following every 4-hour haemodialysis treatment (see Table 1).

Table 1: Pregabalin Dosage Adjustment Based on Renal Function

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

* Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose
\+ Supplementary dose is a single additional dose

Use in Hepatic Impairment

No dosage adjustment is required for patients with hepatic impairment see Section 5.2 PHARMACOKINETIC PROPERTIES, Hepatic Impairment.

Use in Children and Adolescents (<18 years)

The safety and effectiveness of pregabalin has not been established in patients below the age of 18 years with either epilepsy or neuropathic pain.

Use in the Elderly (>65 years)

No dosage adjustment is necessary for elderly patients unless their renal function is compromised (see Table 1).

4.3. CONTRAINDICATIONS

PREGABLIN APOTEX is contraindicated in patients who have demonstrated hypersensitivity to pregabalin or to any of the excipients.

4.4. SPECIAL WARNING AND PRECAUTIONS FOR USE

Hereditary Problems of Galactose Metabolism

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Weight Gain

In the controlled studies, weight gain occurred more frequently in patients treated with pregabalin than in patients treated with placebo. Pregabalin associated weight gain was related to dose and length of exposure, but did not appear to be associated with baseline BMI, gender or age.

In accordance with current clinical practice, some diabetic patients who gain weight on pregabalin treatment may need to adjust hypoglycaemic medications.

Hypersensitivity Reactions

There have been reports in the post-marketing experience of hypersensitivity reactions, including cases of angioedema. Pregabalin should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper airway swelling occur.

Dizziness and Somnolence

Pregabalin causes dizziness and somnolence see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS). In the controlled studies, dizziness and somnolence generally began shortly after initiation of pregabalin and occurred more frequently at higher doses. Dizziness and somnolence were the adverse events most frequently leading to withdrawal (4% each) from controlled studies. In pregabalin-treated patients reporting these adverse events in short-term controlled studies, dizziness persisted until the last dose in 31% and somnolence persisted until the last dose in 46%.

There have also been reports of loss of consciousness, confusion, and mental impairment.

Suicidal Behaviour and Ideation

Antiepileptic drugs (AED), including pregabalin, increase the risk of suicidal thoughts or behaviour in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for 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 randomised 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 drug 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 analysed. 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 2 shows absolute and relative risk by indication for all evaluated AEDs.

Table 2 Risk by indication for Antiepileptic Drugs in the pooled analysis

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

The relative risk for suicidal thoughts or 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 the epilepsy and psychiatric indications.

Anyone considering prescribing pregabalin or any other AED must balance this risk with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and 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.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behaviour and should be advised 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. Behaviours of concern should be reported immediately to the treating doctor.

Monotherapy for Seizure Control

There are insufficient data on seizure control when pregabalin is used as monotherapy once concomitant antiepileptic medical products have been withdrawn in patients where pregabalin was used as add-on therapy.

Substance Misuse, Abuse and Dependence

There have been post-marketing reports of substance misuse and abuse with pregabalin. As with any CNS drug, patients should be carefully evaluated for a history of substance abuse and observed for signs of pregabalin misuse or abuse (e.g. development of tolerance, increase in dose, drug-seeking behavior).

Discontinuation

After discontinuation of short-term and long-term treatment with pregabalin withdrawal symptoms have been observed in some patients. The following events have been mentioned: insomnia, headache, nausea, anxiety, hyperhidrosis and diarrhoea.

Congestive Heart Failure

There have been post-marketing reports of congestive heart failure in some patients receiving pregabalin. Pregabalin should be used with caution in these patients.

Blurred Vision

In controlled studies, a higher proportion of patients treated with pregabalin reported blurred vision than did patients treated with placebo see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS). In the majority of cases, blurred vision resolved with continued dosing. If blurred vision persists, further assessment should be considered.

Post marketing experience with pregabalin has reported transient visual blurring and other changes in visual acuity. Discontinuation of pregabalin may result in resolution or improvement of these visual symptoms.

Peripheral Oedema

In controlled studies, peripheral oedema occurred more frequently in patients treated with pregabalin than in patients treated with placebo see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS). Peripheral oedema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function. There are limited data on the use of pregabalin in patients with congestive heart failure, and pregabalin should be used with caution in these patients.

Creatine Kinase Elevations

Treatment with pregabalin 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, 2% of patients on pregabalin and 1% of placebo patients had a value of creatine kinase at least three times the upper limit of normal. Three pregabalin treated subjects had events reported as rhabdomyolysis in premarketing clinical trials. The relationship between these myopathy events and pregabalin is not completely understood because the cases had documented factors that may have caused or contributed to these events. Pregabalin should be discontinued if myopathy is diagnosed or suspected or if markedly elevated creatine kinase levels occur.

Use in renal impairment

Renal failure is a rare adverse reaction to Pregabalin. Although the effects of discontinuation on the reversibility of renal failure have not been systematically studied, cases of renal failure have been reported and in some cases discontinuation of pregabalin did show reversibility of this adverse reaction.

Use in the elderly

Pregabalin treatment has been associated with dizziness and somnolence, which may increase the occurrence of accidental injury (falls) in the elderly population.

Paediatric use

The safety and effectiveness of pregabalin has not been established in patients below the age of 18 years, with either epilepsy or neuropathic pain.

Effects on Laboratory Tests

Pregabalin is not known to interfere with any laboratory tests. Some changes in clinical laboratory tests have been noted in patients taking Pregabalin (see Table 4 - Investigations).

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Since pregabalin is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (<2% of a dose recovered in urine as metabolites), does not inhibit drug metabolism in vitro, and is not bound to plasma proteins, pregabalin is unlikely to produce, or be subject to, pharmacokinetic interactions.

Accordingly, in *in vivo* studies no clinically relevant pharmacokinetic interactions were observed between pregabalin and phenytoin, carbamazepine, valproic acid, lamotrigine, gabapentin, lorazepam, oxycodone or ethanol. In addition, population pharmacokinetic analysis indicated that the three commonly used drug classes, oral antidiabetics, diuretics and insulin, and the commonly used antiepileptic drugs phenytoin, carbamazepine, valproic acid, lamotrigine, phenobarbital, tiagabine and topiramate, had no clinically significant effect on pregabalin clearance. Similarly, these analyses indicated that pregabalin had no clinically significant effect on the clearance of phenytoin, carbamazepine, valproic acid, lamotrigine, topiramate and phenobarbital.

Co-administration of pregabalin with the oral contraceptives norethisterone and/or ethinyl oestradiol does not influence the steady-state pharmacokinetics of either agent.

Pregabalin may potentiate the effects of ethanol and lorazepam. In controlled clinical trials, multiple oral doses of pregabalin co-administered with oxycodone, lorazepam, or ethanol did not result in clinically important effects on respiration. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone. In post-marketing experience, there are reports of respiratory failure and coma in patients taking pregabalin and other CNS depressant medications.

There are post-marketing reports of events related to reduced lower gastrointestinal tract function (e.g., intestinal obstruction, paralytic ileus, constipation) when pregabalin was co- administered with medications that have the potential to produce constipation, such as opioid analgesics.

No specific pharmacodynamic interaction studies were conducted in elderly volunteers.

4.6. FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Preclinical data:
In male rats, oral administration of high doses of pregabalin resulted in reversible decreased sperm motility and fertility. These were not observed at exposures (plasma AUC) up to 11 times the expected human exposure at the maximum recommended clinical dose of 600 mg/day. There were also no drug-related effects on sperm parameters in a long term monkey study with exposures up to 8 times the expected maximum human exposure. In female rats, oestrus cycles were prolonged by high oral doses of pregabalin, but fertility was unaffected, and an increase in post-implantation loss also occurred. No adverse effects were seen at an exposure approximately 50 times the expected maximum human exposure.

Human data:
In a double-blind, placebo-controlled clinical trial to assess the effect of pregabalin on sperm motility, 30 of 46 healthy male subjects were exposed to pregabalin at 600 mg/day for 3 months. Pregabalin did not exhibit detrimental effects on the reproductive function of healthy male subjects, as measured by semen analysis.

Use in pregnancy (Category B3)

Pregabalin has not been studied in pregnant women and pregabalin should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus. In a pre- and post-natal study in rats, pregabalin treatment resulted in offspring developmental toxicity at exposures (plasma AUC)≥5 times the expected human exposure at the maximum recommended clinical dose of 600 mg/day. Offspring development was unaffected at 2 times the expected maximum human exposure.

Labour and Delivery
The effects of pregabalin on labour and delivery in pregnant women are unknown. In a pre- and post-natal development study in rats, pregabalin prolonged gestation and induced dystocia at exposures (plasma AUC) approximately 50 times the expected human exposure at the maximum recommended clinical dose of 600 mg/day. These effects were not observed at an exposure that was approximately 12 times the expected human exposure.

Teratogenicity
Pregabalin was not teratogenic in mice, rats or rabbits. Foetal developmental toxicity was not observed after treatment of pregnant mice and rabbits with oral doses that resulted in respective pregabalin exposures that were 30 times and 17 times the expected human exposure at the maximum recommended clinical dose of 600 mg/day. Increased foetal skeletal variations were seen in rats at oral doses resulting in exposures > 17 times the expected maximum human exposure, but lower doses were not tested in a full study.

Use in lactation

Pregabalin is excreted in the milk of lactating women see Section 5.2 PHARMACOKINETICS PROPERTIES, Breastfeeding Women. As the safety of pregabalin in infants is not known, breastfeeding is not recommended in women taking pregabalin. A decision must be made whether to discontinue breastfeeding or to discontinue pregabalin therapy, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8. ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The pregabalin clinical programme involved over 9000 patients who were exposed to pregabalin, of whom over 5000 were in double-blind placebo-controlled trials. The clinical efficacy program included patients treated for a maximum of 12 weeks duration.

The most commonly reported adverse reactions were dizziness and somnolence. Adverse reactions were usually mild to moderate in intensity. In all controlled studies, the discontinuation rate due to adverse reactions was 13% for patients receiving pregabalin and 7% for patients receiving placebo. The most common adverse reactions resulting in discontinuation from pregabalin treatment groups were dizziness and somnolence.

The adverse effects listed may also be associated with the underlying disease and concomitant medications.

Table 3: Adverse Effects Reported in At Least 1% of Patients in Pregabalin Controlled Epilepsy and Neuropathic Pain Studies (% of Patients).

MedDRA Preferred Term	Placebo N=1151	Pregabalin (PGB) Total Daily Dose 150 mg/day N=699	300 mg/day N=723	600 mg/day N=918	All PGB* N=258
Dizziness	6.8	13.2	24.5	30.4	21.9
Somnolence	4.6	8.2	13.1	19.5	13.2
Vision blurred	2.1	3.6	4.0	9.0	5.5
Fatigue	3.2	4.3	3.2	8.2	5.3
Weight increased	0.5	3.0	3.9	9.3	5.3
Dry mouth	1.4	3.3	4.6	7.3	5.1
Headache	5.1	3.9	2.9	5.7	4.2
Ataxia	0.6	1.6	2.6	7.6	4.0
Oedema peripheral	1.2	3.4	5.8	3.6	3.8
Balance impaired NOS	0.9	1.6	3.2	5.8	3.6
Diplopia	0.9	2.3	1.9	5.7	3.2
Tremor	1.0	0.9	1.8	5.8	2.9
Constipation	1.3	1.3	2.5	4.1	2.7
Gait abnormal	0.2	0.9	1.8	4.2	2.3
Nausea	4.0	3.0	1.2	2.7	2.2
Confusional state	0.6	1.0	1.7	3.3	1.9

Dysarthria	0.2	0.4	1.2	3.4	1.7
Lethargy	0.1	1.1	1.4	2.5	1.7
Memory impairment	0.5	1.0	0.8	2.8	1.5
Appetite increased NOS	0.3	0.6	0.7	2.9	1.4
Oedema NOS	0.3	0.9	2.1	1.6	1.4
Disturbance in attention	0.7	1.0	0.6	2.4	1.4
Vertigo	0.3	0.7	1.7	1.5	1.3
Diarrhoea NOS	1.4	1.4	0.4	1.1	1.1
Coordination abnormal NOS	0.2	0.3	0.6	2.2	1.1
Peripheral swelling	0.3	0.3	1.4	1.6	1.0

*The All PGB group also includes patients who received pregabalin 50 or 75 mg/day.

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

Table 4: Adverse Drug Reactions from Pregabalin Clinical Trial Experience

SYSTEM ORGAN CLASS	ADVERSE DRUG REACTION
Infections and Infestations	
Common	Nasopharyngitis
Blood and lymphatic system disorders	
Uncommon	Neutropenia
Metabolism and nutrition disorders	
Common	Appetite increased
Uncommon	Anorexia, hypoglycaemia
Psychiatric disorders	
Common	Euphoric mood, confusion, irritability, depression, disorientation, insomnia, libido decreased
Uncommon	Hallucination, restlessness, agitation, depressed mood, elevated mood, mood swings, depersonalisation, abnormal dreams, word finding difficulty, libido increased, anorgasmia
Rare	Panic attack, disinhibition, apathy
Nervous system disorders	
Very common	Dizziness, somnolence
Common	Ataxia, co-ordination abnormal, tremor, dysarthria, amnesia, memory impairment, disturbance in attention, paraesthesia, hypoaesthesia, sedation, balance disorder, lethargy
Uncommon	Syncope, myoclonus, psychomotor hyperactivity, dyskinesia, dizziness postural, intention tremor, nystagmus, cognitive disorder, speech disorder, hyporeflexia, hyperaesthesia, burning sensation
Rare	Stupor, parosmia, hypokinesia, ageusia, dysgraphia, encephalopathy, muscle spasticity

Eye disorders	
Common	Vision blurred, diplopia
Uncommon	Peripheral vision loss, visual disturbance, eye swelling, visual field defect, visual acuity reduced, eye pain, asthenopia, photopsia, dry eye, lacrimation increased, eye irritation
Rare	Oscillopsia, altered visual depth perception, mydriasis, strabismus, visual brightness
Ear and labyrinth disorders	
Common	Vertigo
Uncommon	Hyperacusis
Cardiac disorders	
Uncommon	Tachycardia, atrioventricular block first degree, sinus bradycardia
Rare	Sinus tachycardia, sinus arrhythmia
Vascular disorders	
Uncommon	Hypotension, hypertension, hot flushes, flushing, peripheral coldness
Rare	Petechiae
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring
Rare	Throat tightness, nasal dryness
Gastrointestinal disorders	
Common	Vomiting, constipation, flatulence, abdominal distension, dry mouth
Uncommon	Gastro-oesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral
Rare	Ascites, pancreatitis, dysphagia
Skin and subcutaneous tissue disorders	
Uncommon	Rash papular, urticaria, sweating
Rare	Cold sweat, Henoch-Schonlein purpura
Musculoskeletal and connective tissue disorders	
Common	Muscle cramp, arthralgia, back pain, pain in limb, cervical spasm
Uncommon	Joint swelling, myalgia, muscle twitching, neck pain, muscle stiffness
Rare	Rhabdomyolysis
Renal and urinary disorders	
Uncommon	Urinary incontinence, dysuria
Rare	Renal failure, oliguria
Reproductive system and breast disorders	
Uncommon	Erectile dysfunction, sexual dysfunction, ejaculation delayed, dysmenorrhoea
Rare	Breast pain, amenorrhoea, breast discharge, breast enlargement

General disorders and administration site conditions	
Common	Oedema peripheral, oedema, gait abnormal, fall, feeling drunk, feeling abnormal, fatigue
Uncommon	Generalised oedema, chest tightness, pain, pyrexia, thirst, chills, asthenia
Investigations	
Common	Weight increased
Uncommon	Blood creatine phosphokinase increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood glucose increased, platelet count decreased, blood potassium decreased, weight decreased
Rare	White blood cell count decreased, blood

Post-Marketing Experience

The following adverse drug reactions were reported during post-marketing surveillance:

Immune system disorders: Uncommon: Hypersensitivity; Rare: Angioedema, allergic reaction.

Nervous system disorders: Very common: Headache; Uncommon: Loss of consciousness, mental impairment.

Cardiac disorders: Rare: Congestive heart failure.

Eye disorders: Rare: Keratitis.

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

General disorders and administration site conditions: Uncommon: Malaise.

Skin and subcutaneous tissue disorders: Uncommon: Face swelling, pruritis, alopecia

Renal and urinary disorders: Rare: Urinary retention.

Reproductive system and breast disorders: Rare: Gynaecomastia.

Respiratory, thoracic and mediastinal disorders: Rare: Pulmonary oedema.

Vital Signs

No consistent changes in vital signs have been seen in patients taking Pregabalin. Changes in vital signs reported in controlled clinical trials are shown in Table 4.

Elderly (>65 years)

In a total of 998 elderly patients, no overall differences in safety were observed compared with patients less than 65 years of age.

Reporting suspected adverse reactions after registration of the medical 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 at http://www.tga.gov.au/reporting-problems.

4.9. OVERDOSE

Symptoms

In overdoses up to 15 g, no unexpected adverse effects were reported.

In post-marketing experience, the most commonly reported adverse events observed when pregabalin was taken in overdose included affective disorder, somnolence, confusional state, depression, agitation and restlessness.

Management

There is no specific antidote for pregabalin. Treatment of pregabalin overdose should be symptomatic and supportive.

Consider administration of activated charcoal in the event of a potentially toxic ingestion. Activated charcoal is most effective when administered within one hour of ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected.

Haemodialysis may be useful in patients with severe toxicity or those with significant renal impairment (see Dosage and Administration, Use in Renal Impairment). Standard haemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours). Emesis is not recommended because of the potential for CNS depression and seizures.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Mechanism of action

In vitro studies show that pregabalin binds to an auxiliary subunit ($\alpha_2\delta$ protein) of voltage-gated calcium channels in the central nervous system, potently displacing [3H]-gabapentin. Two lines of evidence indicate that binding of pregabalin to the $\alpha_2\delta$ site is required for anticonvulsant activity in animal models: (1) Studies with the inactive R-enantiomer and other structural derivatives of pregabalin and (2) Studies of pregabalin in mutant mice with defective drug binding to the $\alpha_2\delta$ protein. In addition, pregabalin reduces the release of several neurotransmitters, including glutamate, noradrenaline and substance P. The significance of these effects for the clinical pharmacology of pregabalin is not known.

Pregabalin does not show affinity for receptor sites or alter responses associated with the action of several common drugs for treating seizures or pain. Pregabalin does not interact with either GABAA or GABAB receptors; it is not converted metabolically into GABA or a GABA agonist; it is not an inhibitor of acute GABA uptake or degradation.

Pregabalin prevents pain-related behaviours in animal models of neuropathic and post-surgical pain, including hyperalgesia and allodynia.

Pregabalin shows efficacy in animal models of seizures including: maximal electroshock tonic extensor seizures in mice or rats; threshold clonic seizures from pentylenetetrazol, behavioural and electrographic seizures in hippocampal kindled rats; and tonic and clonic seizures in DBA/2 audiogenic mice. Pregabalin does not reduce the incidence of spontaneous absence seizures in Genetic Absence Epilepsy in Rats from Strasbourg (GAERS).

Pharmacokinetics

Pregabalin steady-state pharmacokinetics are similar in healthy volunteers, patients with epilepsy receiving anti-epileptic drugs and patients with chronic pain.

Clinical trials

Neuropathic Pain

The effectiveness of pregabalin for the management of neuropathic pain was investigated in 11 double blind, placebo-controlled, multi-centre studies with either twice a day (BID) or three times a day (TID) dosing.

The analysis of the primary efficacy variable is provided below for each study within the diabetic peripheral neuropathy, and post-herpetic neuralgia population.

The overall picture of the primary efficacy variable across populations is confirmed by the responder rates. The response rates for a 30% reduction in pain score showed that the proportion of patients responding increased with increasing doses, from 34 - 49% at 150 mg per day to 54 - 65% at 600 mg per day, compared with 19 - 45% for placebo. The response rates for a 50% reduction in pain score showed that the proportion of patients responding increased with increasing doses, from 19 - 34% at 150 mg per day to 39 - 50% at 600 mg per day, compared with 8 – 30% for placebo.

Up to 88% of patients treated with 300 or 600 mg/day pregabalin reported benefit, compared with 26 – 66% for placebo, as measured by an improvement in the Patient Global Impressions of Change (PGIC) score. The PGIC is a patient-rated instrument that measures change in a patient's overall status on a scale ranging from 1 (very much improved) to 7 (very much worse).

A significant reduction in pain was seen by Week 1 and maintained relative to placebo throughout the treatment. Significant reductions in sleep interference were seen, when patients were treated with pregabalin for neuropathic pain, by Week 1 and maintained throughout the treatment.

Diabetic Peripheral Neuropathy (DPN)

The effectiveness of pregabalin for the management of neuropathic pain was investigated in 6 double blind, placebo-controlled, multi-centre studies with either twice a day (BID) or three times a day (TID) dosing. A total of 1525 patients were enrolled in the 6 studies. To enter the study patients had to have moderate to severe pain. The mean age of patients in these studies was 59 years (range 21 – 85 years), 89% of patients had Type II diabetes mellitus with an average HbA1c of 8.9%.

In the 5 completed studies, the average age was 59 years, the duration of diabetes was 11 years, and the average baseline pain score was 6.5. The use of concurrent medication that may affect the assessments was prohibited. Antidiabetic medication was required to be stable and constant during the study.

Table 5: Results of the Primary Outcome (Endpoint Mean Pain Scores) for Diabetic Peripheral Neuropathy Studies.

Study/Treatment Group	Treatment Comparisons				
	N	Mean Baseline	Mean Endpoint	Difference	95% confidence interval
DPN Pain Model				(Pregabalin – Placebo)	
Study 014 TID [6 weeks] N=246					
Placebo (n=85)	82	6.9	5.55		
Pregabalin 150 mg/day (n=79)	79	6.5	5.11	-0.44	(-1.08, 0.20)
Pregabalin 600 mg/day (n=82)	82	6.7	4.29	-1.26	(-1.89, -0.64)
Study 029 TID [5 weeks] N=337					
Placebo (n=97)	97	6.6	5.06		
Pregabalin 75 mg/day (n=77)	77	6.7	4.91	-0.15	(-0.76, 0.46)
Pregabalin 300 mg/day (n=81)	81	6.2	3.80	-1.26	(-1.86, -0.65)
Pregabalin 600 mg/day (n=82)	81	6.2	3.60	-1.45	(-2.06, -0.85)
Study 040 TID [8 weeks] N=167					
Placebo (n=81)	80	6.3	4.60		
Pregabalin 600 mg/day (n=86)	86	6.9	3.96	-0.64	(-1.37, 0.08)
Study 131 TID [8 weeks] N=146					
Placebo (n=70)	69	6.1	5.46		
Pregabalin 300 mg/day (n=76)	75	6.5	3.99	-1.47	(-2.19, -0.75)
Study 149 BID [12 weeks] N=395					
Placebo (n=96)	93	6.4	4.66		
Pregabalin 150 mg/day (n=99)	96	6.2	4.33	-0.33	(-0.94, 0.28)
Pregabalin 300 mg/day (n=99)	96	6.4	4.48	-0.18	(-0.79, 0.43)
Pregabalin 300/600 mg/day* (n=101)	98	6.6	3.69	-0.97	(-1.58, -0.36)
Study 173 BID [12 weeks] N=147					
Placebo (n=31)	29	6.3	5.33		
Pregabalin 150 mg/day (n=34)	34	6.3	4.77	-0.55	(-1.54, 0.43)
Pregabalin 300 mg/day (n=44)	43	6.8	4.99	-0.34	(-1.29, 0.61)
Pregabalin 300/600 mg/day* (n=39)	38	6.7	4.09	-1.24	(-2.21, -0.27)

*Patients randomised to the 300/600 mg/day pregabalin group received either 300 or 600 mg/day based on their CL_{Cr}.

Post-herpetic Neuralgia (PHN)

The effectiveness of pregabalin for the management of neuropathic pain was investigated in 5 double blind, placebo-controlled, multi-centre studies with either twice a day (BID) or three times a day (TID) dosing. A total of 1250 patients were enrolled in the 5 studies. To enter the study patients had to have moderate to severe pain for ≥ 3 months (or ≥ 6 months in one study). The mean duration of PHN for patients in these studies was 3 years (range < 1 – 22 years).

In the 4 completed studies, the average age was 71 years, the average duration of PHN was 38 months, and the average baseline pain score was 6.6. Concomitant use of analgesics and antidepressants was allowed, provided the regimen was stable and in place at the time of randomization.

Table 6. Results of the Primary Outcome (Endpoint Mean Pain Scores) for Post-herpetic Neuralgia Studies

Study/Treatment	N	Mean Baseline	Mean endpoint	Treatment Comparisons: Difference	Treatment Comparisons: 95% confidence interval
PHN Pain Model				(Pregabalin - Placebo)	
Study 030 TID [5 weeks] N=255					
Placebo (n=88)	87	6.6	5.59		
Pregabalin 75 mg/day (n=84)	83	6.7	5.46	-0.14	(-0.71, 0.43)
Pregabalin 150 mg/day (n=83)	82	6.4	5.52	-0.07	(-0.64, 0.50)
Study 045 TID [8 weeks] N=238					
Placebo (n=81)	81	6.6	6.33		
Pregabalin 150 mg/day (n=81)	81	6.9	5.14	-1.20	(-1.81, -0.58)
Pregabalin 300 mg/day (n=76)	76	7.0	4.76	-1.57	(-2.20, -0.95)
Study 127 TID [8 weeks] N=173					
Placebo (n=84)	84	6.4	5.29		
Pregabalin 300/600 mg/day* (n=89)	88	6.3	3.60	-1.69	(-2.33, -1.05)
Study 132 BID [12 weeks†] N=216					
Placebo (n=52)	52	6.0	6.23		
Pregabalin 150 mg/day (n=51)	51	6.9	5.05	-1.18	(-1.90, -0.46)
Pregabalin 300 mg/day (n=62)	62	6.6	4.90	-1.33	(-2.01, -0.65)
Pregabalin 300/600 mg/day* (n=51)	50	6.6	4.26	-2.02	(-2.74, -1.31)
Study 196 BID [13 weeks] N=368					
Placebo (n=93)	93	6.9	6.14		
Pregabalin 150 mg/day (n=87)	87	6.4	5.26	-0.88	(-1.53, -0.23)
Pregabalin 300 mg/day (n=98)	98	6.7	5.07	-1.07	(-1.70, -0.45)
Pregabalin 300/600 mg/day* (n=90)	88	6.7	4.35	-1.79	(-2.43, -1.15)

*Patients randomised to the 300/600 mg/day pregabalin group received either 300 or 600 mg/day based on their CL_{cr}.

†Study stopped prematurely.

Epilepsy

The efficacy of pregabalin as adjunctive therapy was investigated in three 12-week, randomised, double blind, placebo controlled, multi-centre studies involving 1052 patients, with BID and/or TID dosing. Patients had refractory partial seizures with or without secondary generalisation and had mean baseline seizure rates of 21-22 and median baseline seizure rates of 10-12 seizures per 28 days.

The primary efficacy measure in all studies was based on seizure reduction as analysed by response ratio (RRatio), a measure of change defined as [(T - B)/(T + B)] x 100, where B is the patient's baseline seizure frequency and T is the patient's seizure frequency during treatment. The RRatio is distributed within the range -100 to +100. A zero value indicates no change and a complete elimination of seizures would give a value of -100. Responder rate was defined as the proportion of patients who have a ≥ 50% reduction in partial seizure frequency during treatment as compared to baseline.

Table 7. Results of the Primary Outcomes (RRatio and Responder Rate) for Epilepsy Studies

Study/Treatment Group	RRatio								Responder Rate				
					Treatment Difference Between Pregabalin and Placebo					Treatment difference between Pregabalin and Placebo			
	N	Mean	SD	Median	Mean	(SE)	p Value	95% CI	Responder (%)	%	(SE)	p Value	95% CI
Study 009 BID/TID													
Placebo	98	0.6	28.8	-0.4					9 (9.2)				
Pregabalin 600 mg/day BID	103	-28.4	36.7	-21.7	-29.0	(5.0)	≤0.0001 *	-38.9, -19.0	44 (42.7)	33.5	(5.7)	≤0.001*	22.4, 44.7
Pregabalin 600 mg/day TID	111	-36.1	40	-31.7	-36.7	(5.0)	≤0.0001 *	-46.4, -27.0	54 (48.7)	39.5	(5.6)	≤0.001*	28.5, 50.4
Study 011 TID													
Placebo	96	0.9	26	0.7					6 (6.2)				
Pregabalin 150 mg/day	99	-11.5	22-9	-9	-12.4	(4.1)	0.0007*	-20.5, -4.3	14 (14.1)	7.9	(4.3)	0.087	-0.5, 16.3
Pregabalin 600 mg/day	92	-31.4	36-3	-27-1	-32.3	(4.2)	≤0.0001 *	-40.6, -24.0	40 (43.5)	37.2	(5.7)	≤0.001*	26.0, 48.5
Study 034 BID													
Placebo	100	-3.8	25.6	0					14 (14.0)				
Pregabalin 50 mg/day	88	-6.2	23.7	-4.5	-2.3	(4.8)	0.4232	-11.7, 7.1	13 (14.8)	0.8	(5.1)	0.840	-9.3, 10.8
Pregabalin 150 mg/day	86	-20.5	29.6	-21	-16.6	(4.8)	≤0.0001 *	-26.1, -7.2	27 (31.4)	17.4	(6.1)	0.006*	5.5, 29.3
Pregabalin 300 mg/day	90	-27.8	36.5	-22.5	-24.0	(4.8)	≤0.0001 *	-33.3, -14.6	36 (40.0)	26.0	(6.2)	≤0.001*	13.8, 38.2
Pregabalin 600 mg/day	89	-37.4	44.4	-34.1	-33.5	(4.8)	≤0.0001 *	-42.9, -24.1	45 (50.6)	36.6	(6.3)	≤0.001*	24.1, 49.0

SD = Standard deviation; SE = Standard error; CI = Confidence interval

* Statistically significant based on Hochberg's (Study 009) or the Ruberg (Studies 011 and 034) procedure ($\alpha = 0.049$ for Studies 009 and 034, $\alpha = 0.05$ for Study 011).

A significant reduction in seizure frequency was observed by Week 1. Overall, there was a significant reduction in seizure frequency over the 12-week treatment period.

Long-term efficacy data in support of the chronic use of pregabalin for the treatment of patients with partial seizures were provided by four open label extension studies. These studies permitted pregabalin as adjunctive therapy with marketed AEDs. Data from the long-term studies support the long-term use of pregabalin for the treatment of patients with partial seizures, as well as demonstrating the maintenance of effect over the long term.

5.2. PHARMACOKINETIC PROPERTIES

Absorption

Pregabalin is rapidly absorbed when administered in the fasted state, with peak plasma concentrations occurring within 1 hour following both single and multiple dose administration. Pregabalin oral bioavailability is estimated to be ≥ 90% and is independent of dose. Following repeated administration, steady state is achieved within 24–48 hours. The rate of pregabalin absorption is decreased when given with food resulting in a decrease in C_{max} by approximately 25–30% and a delay in t_{max} to approximately 2.5 hours. However, administration of pregabalin with food has no clinically significant effect on the extent of pregabalin bioavailability.

Distribution

In preclinical studies, pregabalin has been shown to cross the blood brain barrier in mice, rats and monkeys. Pregabalin has been shown to cross the placenta in rats and is present in the milk of lactating rats. In humans, the apparent volume of distribution of pregabalin following oral administration is approximately 0.56 L/kg. Pregabalin is not bound to plasma proteins. At clinical doses of 150 and 600 mg/day, the average steady-state plasma pregabalin concentrations were approximately 1.5 and 6.0 µg/mL, respectively.

Metabolism

Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabelled pregabalin, approximately 98% of the radioactivity recovered in the urine was unchanged pregabalin. The N-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0.9% of the dose. In preclinical studies, there was no indication of racemization of pregabalin *S*-enantiomer to the *R*-enantiomer.

Excretion

Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. Renal clearance (CLcr) derived from Phase I studies was 73 mL/min.

Pregabalin mean elimination half-life is 6.3 hours. Pregabalin plasma clearance and renal clearance are directly proportional to creatinine clearance (see Special Populations, Renal Impairment).

Pregabalin clearance is reduced in patients with impaired renal function see Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Use in Renal Impairment, Table 1.

Linearity/Non-linearity

Pregabalin pharmacokinetics are linear over the recommended daily dose range. Inter-subject pharmacokinetic variability for pregabalin is low (<20%). Multiple dose pharmacokinetics are predictable from single dose data.

Special Populations

Race
Population pharmacokinetic analyses of the Phase 2/3 studies in patients with chronic pain, general anxiety disorder (GAD) or partial seizures showed that the relationship between daily dose and pregabalin exposure is similar among Caucasians, Blacks and Hispanics.

Gender
Population pharmacokinetic analyses of the Phase 2/3 studies in patients with chronic pain, GAD or partial seizures showed that the relationship between daily dose and pregabalin drug exposure is similar between genders when adjusted for gender-related differences in CL_{cr}.

Renal Impairment
Pregabalin clearance is directly proportional to creatinine clearance. In addition, pregabalin is effectively removed from plasma by haemodialysis (following a 4-hour haemodialysis treatment, plasma pregabalin concentrations are reduced by approximately 50%). Because renal elimination is the major elimination pathway, dosage reduction in patients with renal impairment and dosage supplementation following haemodialysis is necessary Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Use in Renal Impairment, Table 1.

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

Elderly (>65 years)
Pregabalin clearance tends to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with decreases in creatinine clearance associated with increasing age. Reduction of pregabalin dose may be required in patients who have age related compromised renal function Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Use in Renal Impairment, Table 1.

Children and Adolescents (<18 years)
No specific pharmacokinetic studies have been undertaken in patients < 18 years of age.

Breastfeeding Women
The pharmacokinetics of 150 mg pregabalin given every 12 hours (300 mg daily dose) was evaluated in 10 lactating women who were at least 12 weeks postpartum. Lactation had little to no influence on pregabalin pharmacokinetics. Pregabalin was excreted into breast milk with average steady-state concentrations approximately 76% of those in maternal plasma. The estimated average daily infant dose of pregabalin from breast milk (assuming mean milk consumption of 150 mL/kg/day) was 0.31 mg/kg/day, which on a mg/kg basis would be approximately 7% of the maternal dose see Section 4.6 FERTILITY, PREGNANCY AND LACTATION, Use in Lactation.

5.3. PRECLINICAL SAFETY DATA

Genotoxicity

Pregabalin is not genotoxic based on results of *in vitro* and *in vivo* tests. It was not mutagenic in bacteria or in mammalian cells *in vitro*, not clastogenic in mammalian systems *in vitro* and *in vivo*, and did not induce unscheduled DNA synthesis in mouse or rat hepatocytes.

Carcinogenicity

Two-year carcinogenicity studies with pregabalin were conducted in rats and mice. No increased incidence of tumours was observed in rats at exposures (plasma AUC) up to 25 times the expected human exposure at the maximum recommended clinical dose of 600 mg/day. In mice, no increased incidence of tumours was found at exposures similar to the expected maximum human exposure, but an increased incidence of haemangiosarcoma was observed at exposures 6 to 33 times the expected maximum human exposure. The precise non-genotoxic mechanism of pregabalin-induced tumour formation is not fully characterised. However, available data show that platelet changes associated with the formation of this tumour in mice are not seen in rats, monkeys or humans. Although long-term data in humans are limited, these findings in mice are thought not to pose a risk to humans.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

PREGABLIN APOTEX 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg capsules contain the following inactive ingredients: lactose monohydrate, pregelatinised maize starch and purified talc.

The capsule shells consist of gelatin, titanium dioxide, iron oxide black CI77499 and Capsugel Ink 10A1 Black Ink (ARTG 109522) or Capsugel Ink 10A2 Black Ink (ARTG 109521). The 75 mg, 100 mg, 200 mg, 225 mg and 300 mg capsules also contain iron oxide red CI77491 and iron oxide yellow CI77492.

6.2. INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3. SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5. NATURE AND CONTENTS OF CONTAINER

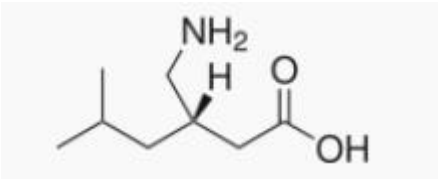
Available in PVC/aluminium blister packs of 56 capsules. Non-marketed pack sizes: 14, 20 and 60 capsules.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7. PHYSIOCHEMICAL PROPERTIES

Chemical structure:



Chemical name: (*S*)-3-(aminomethyl)-5-methylhexanoic acid

Molecular formula: $C_8H_{17}NO_2$

Molecular weight: 159.23

CAS number: 148553-50-8

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8. SPONSOR

Southern Cross Pharma Pty Ltd

Suite 5/118 Church Street

Hawthorn VIC 3122

Distributor

16 Giffnock Avenue

Macquarie Park NSW 2113

Australia

9. DATE OF FIRST APPROVAL

14 February 2017

10. DATE OF REVISION

25 July 2018

Summary table of changes

Section Changed	Summary of new Information
All	PI updated to new format