For the use only of a Registered Medical Practitioner
or a Hospital or a Laboratory

Pregabalin Capsules I.P.

LYRICA®

1 GENERIC NAME

Pregabalin Capsules I.P.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard gelatin capsule contains Pregabalin I.P. equivalent to Pregabalin 25 mg or 50 mg or 75 mg or 150 mg.

List of Excipients

Lactose monohydrate, Maize starch and Talc.

3 DOSAGE FORM AND STRENGTH

Hard Gelatin Capsule 25 mg or 50 mg 75 mg or 150 mg

4 CLINICAL PARTICULARS

4.1 Therapeutic indication

Neuropathic pain

Pregabalin is indicated for the treatment of neuropathic pain in adults.

Fibromyalgia

Pregabalin is indicated for the management of fibromyalgia.

4.2 Posology and method of administration

Posology

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

Neuropathic pain

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

Fibromyalgia

The recommended dose of pregabalin is 300 to 450 mg/day. Dosing should begin at 75 mg two times a day (150 mg/day) and may be increased to 150 mg two times a day (300 mg/day) within one week based on efficacy and tolerability. Patients who do not experience sufficient benefit with 300 mg/day may be further increased to 150 mg three times a day (450 mg/day). Although pregabalin was also studied at 600 mg/day, there is no evidence that this dose confers additional benefit and that this dose was less tolerated.

Discontinuation of pregabalin

In accordance with current clinical practice, if pregabalin has to be discontinued, it is recommended this should be done gradually over a minimum of 1 week independent of the indication (see sections 4.4 and 4.8).

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 5.3), dose reduction in patients with compromised renal function must be individualised according to creatinine clearance (CL_{cr}), as indicated in Table 1 determined using the following formula:

$$\text{CLcr(ml/min)} = \left[\frac{1.23\text{x [140-age (years)] x weight (kg)}}{\text{serum creatinine (µmol/l)}}\right] \text{(x 0.85for female patients)}$$

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 Dose 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	BID or TID
≥30 - <60	75	300	BID or TID
≥15 - <30	25 - 50	150	Once Daily or BID
<15	25	75	Once Daily
Supplementary dosage following haemodialysis (mg)			
	25	100	Single dose+

TID = Three divided doses. BID = Two divided doses.

* Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose.

+ Supplementary dose is a single additional dose.

Hepatic impairment

No dose adjustment is required for patients with hepatic impairment (see section 5.3).

Paediatric population

The safety and efficacy of Pregabalin in children below the age of 12 years and in adolescents (12-17 years of age) have not been established. Currently available data are described in sections 4.8, 5.2 and 5.3 but no recommendation on a posology can be made.

Elderly

Elderly patients may require a dose reduction of pregabalin due to a decreased renal function (see section 5.3).

Method of administration

Pregabalin may be taken with or without food.

Pregabalin is for oral use only.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 2.

4.4 Special warnings and precautions for use

Diabetic patients

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

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.

Severe cutaneous adverse reactions (SCARs)

SCARs including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported rarely in association with pregabalin treatment. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, pregabalin should be withdrawn immediately and an alternative treatment considered (as appropriate).

Dizziness, somnolence, loss of consciousness, confusion and mental impairment

Pregabalin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in the elderly population. There have also been post marketing reports of loss of consciousness, confusion, and mental impairment. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medicinal product.

Vision-related effects

In controlled trials, a higher proportion of patients treated with pregabalin reported blurred vision than did patients treated with placebo which resolved in a majority of cases with continued dosing. In the clinical studies where ophthalmologic testing was conducted, the incidence of visual acuity reduction and visual field changes was greater in pregabalin-treated patients than in placebo-treated patients; the incidence of fundoscopic changes was greater in placebo-treated patients (see section 5.1).

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

Renal failure

Cases of renal failure have been reported and in some cases discontinuation of pregabalin did show reversibility of this adverse reaction.

Withdrawal of concomitant anti-epileptic medicinal products

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

Withdrawal symptoms

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, diarrhoea, flu syndrome, nervousness, depression, pain, convulsion, hyperhidrosis and dizziness, suggestive of physical dependence. The patient should be informed about this at the start of the treatment.

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

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

Congestive heart failure

There have been post-marketing reports of congestive heart failure in some patients receiving pregabalin. These reactions are mostly seen in elderly cardiovascular compromised patients during pregabalin treatment for a neuropathic indication. Pregabalin should be used with caution in these patients. Discontinuation of pregabalin may resolve the reaction.

Treatment of central neuropathic pain due to spinal cord injury

In the treatment of central neuropathic pain due to spinal cord injury the incidence of adverse reactions in general, central nervous system adverse reactions and especially somnolence was increased. This may be attributed to an additive effect due to concomitant medicinal products (e.g., anti-spasticity agents) needed for this condition. This should be considered when prescribing pregabalin in this condition.

Respiratory depression

There have been reports of severe respiratory depression in relation to pregabalin use. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment, concomitant use of CNS depressants and the elderly may be at higher risk of experiencing this severe adverse reaction. Dose adjustments may be necessary in these patients (see section 4.2).

Suicidal ideation and behaviour

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled studies of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for pregabalin. Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Reduced lower gastrointestinal tract function

There are postmarketing 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. When pregabalin and opioids will be used in combination, measures to prevent constipation may be considered (especially in female patients and elderly).

Concomitant use with opioids

Caution is advised when prescribing pregabalin concomitantly with opioids due to risk of CNS depression (see section 4.5). In a case control study of opioid users, those patients who took pregabalin concomitantly with an opioid had an increased risk for opioid-related death compared to opioid use alone (adjusted odds ratio [aOR], 1.68 [95% CI, 1.19 – 2.36]). This increased risk was observed at low doses of pregabalin (≤300 mg, aOR 1.52 [95% CI, 1.04 – 2.22]) and there was a trend for a greater risk at high doses of pregabalin (>300 mg, aOR 2.51 [95% CI, 1.24 – 5.06]).

Misuse, abuse potential or dependence

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

Withdrawal symptoms

After discontinuation of short-term and long-term treatment with pregabalin, withdrawal symptoms have been observed. The following symptoms have been reported: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, nervousness, depression, pain, convulsion, hyperhidrosis and dizziness. The occurrence of withdrawal symptoms following discontinuation of pregabalin may indicate drug dependence. The patient should be informed about this at the start of the treatment. If pregabalin should be discontinued, it is recommended this should be done gradually over a minimum of 1 week independent of the indication.

Convulsions, including status epilepticus and grand mal convulsions, may occur during pregabalin use or shortly after discontinuing pregabalin. Concerning discontinuation of long-term treatment of pregabalin, data suggest that the incidence and severity of withdrawal symptoms may be dose-related.

Encephalopathy

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

Women of childbearing potential/Contraception

Pregabalin Pfizer use in the first-trimester of pregnancy may cause major birth defects in the unborn child. Pregabalin should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus. Women of childbearing potential have to use effective contraception during treatment (see section 4.6).

Lactose intolerance

Pregabalin contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium content

Pregabalin contains less than 1 mmol sodium (23 mg) per hard capsule. Patients on low sodium diets can be informed that this medicinal product is essentially 'sodium-free'.

4.5 Drugs 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, it is unlikely to produce, or be subject to, pharmacokinetic interactions.

In vivo studies and population pharmacokinetic analysis

Accordingly, in *in vivo* studies no clinically relevant pharmacokinetic interactions were observed between pregabalin and phenytoin, carbamazepine, valproic acid, lamotrigine, gabapentin, lorazepam, oxycodone or ethanol. Population pharmacokinetic analysis indicated that oral antidiabetics, diuretics, insulin, phenobarbital, tiagabine and topiramate had no clinically significant effect on pregabalin clearance.

Oral contraceptives, norethisterone and/or ethinyl oestradiol

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

Central nervous system influencing medical products

Pregabalin may potentiate the effects of ethanol and lorazepam.

In the postmarketing experience, there are reports of respiratory failure, coma and deaths in patients taking pregabalin and opioids and/or other central nervous system (CNS) depressant medicinal products. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone.

Interactions and the elderly

No specific pharmacodynamic interaction studies were conducted in elderly volunteers. Interaction studies have only been performed in adults.

4.6 Use in special populations

Women of childbearing potential/Contraception

Women of childbearing potential have to use effective contraception during treatment (see section 4.4).

Pregnancy

Studies in animals have shown reproductive toxicity (see section 6.1).

Pregabalin has been shown to cross the placenta in rats (see section 5.3). Pregabalin may cross the human placenta.

Major congenital malformations

Data from a Nordic observational study of more than 2700 pregnancies exposed to pregabalin in the first trimester showed a higher prevalence of major congenital malformations (MCM) among the paediatric population (live or stillborn) exposed to pregabalin compared to the unexposed population (5.9% vs. 4.1%).

The risk of MCM among the paediatric population exposed to pregabalin in the first trimester was slightly higher compared to unexposed population (adjusted prevalence ratio and 95% confidence interval: 1.14 (0.96-1.35)), and compared to population exposed to lamotrigine (1.29 (1.01–1.65)) or to duloxetine (1.39 (1.07–1.82)).

The analyses on specific malformations showed higher risks for malformations of the nervous system, the eye, orofacial clefts, urinary malformations and genital malformations, but numbers were small and estimates imprecise.

Pregabalin should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the foetus).

Breast-feeding

Pregabalin is excreted into human milk (see section 5.3). The effect of pregabalin on newborns/infants is unknown. A decision must be made whether to discontinue breast-feeding or to discontinue pregabalin therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility

There are no clinical data on the effects of pregabalin on female fertility.

In a clinical trial to assess the effect of pregabalin on sperm motility, healthy male subjects were exposed to pregabalin at a dose of 600 mg/day. After 3 months of treatment, there were no effects on sperm motility.

A fertility study in female rats has shown adverse reproductive effects. Fertility studies in male rats have shown adverse reproductive and developmental effects. The clinical relevance of these findings is unknown (see section 6.1).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The pregabalin clinical programme involved over 8,900 patients exposed to pregabalin, of whom over 5,600 were in double-blind placebo controlled trials. The most commonly reported adverse reactions were dizziness and somnolence. Adverse reactions were usually mild to moderate in intensity. In all controlled studies, the discontinuation rate due to adverse reactions was 12% for patients receiving pregabalin and 5% for patients receiving placebo. The most common adverse reactions resulting in discontinuation from pregabalin treatment groups were dizziness and somnolence.

In table 2 below all adverse reactions, which occurred at an incidence greater than placebo and in more than one patient, are listed by class and frequency (very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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

In the treatment of central neuropathic pain due to spinal cord injury the incidence of adverse reactions in general, CNS adverse reactions and especially somnolence was increased (see section 4.4).

Additional reactions reported from post marketing experience are included in italics in the list below.

Table 2. Pregabalin Adverse Drug Reactions

System Organ Class	Adverse drug reactions
Immune system disorders	
Uncommon	Hypersensitivity
Rare	Angioedema, allergic reaction
Metabolism and nutrition disorders	
Common	Appetite increased
Uncommon	Anorexia, hypoglycaemia
Psychiatric disorders	
Common	Euphoric mood, confusion, irritability, disorientation, insomnia, libido decreased
Uncommon	Hallucination, panic attack, restlessness, agitation, depression, depressed mood, elevated mood, *aggression*, mood swings, depersonalisation, word-finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy
Rare	Disinhibition
Nervous system disorders	
Very Common	Dizziness, somnolence, headache
Common	Ataxia, coordination abnormal, tremor, dysarthria, amnesia, memory impairment, disturbance in attention, paraesthesia, hypoaesthesia, sedation, balance disorder, lethargy
Uncommon	Syncope, stupor, myoclonus, *loss of consciousness*, psychomotor hyperactivity, dyskinesia, dizziness postural, intention tremor, nystagmus, cognitive disorder, *mental impairment*, speech disorder, hyporeflexia, hyperaesthesia, burning sensation, ageusia, *malaise*
Rare	*Convulsions*, parosmia, hypokinesia, dysgraphia, parkinsonism
Eye disorders	
Common	Vision blurred, diplopia
Uncommon	Peripheral vision loss, visual disturbance, eye swelling, visual field defect, visual acuity reduced, eye pain, asthenopia, photopsia, dry eye, lacrimation increased, eye irritation
Rare	*Vision loss*, *keratitis*, oscillopsia, altered visual depth perception, mydriasis, strabismus, visual brightness
Ear and labyrinth disorders	
Common	Vertigo
Uncommon	Hyperacusis
Cardiac disorders	
Uncommon	Tachycardia, atrioventricular block first degree, sinus bradycardia, *congestive heart failure*
Rare	*QT prolongation*, sinus tachycardia, sinus arrhythmia

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Supplier SAP No.	N/A				
Sign-offs					
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Vascular disorders	
Uncommon	Hypotension, hypertension, hot flushes, flushing, peripheral coldness
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness
Rare	*Pulmonary oedema,* throat tightness
Not known	Respiratory depression
Gastrointestinal disorders	
Common	Vomiting, *nausea*, constipation, *diarrhoea*, flatulence, abdominal distension, dry mouth
Uncommon	Gastrooesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral
Rare	Ascites, pancreatitis, *swollen tongue*, dysphagia
Hepatobiliary disorders	
Uncommon	Elevated liver enzymes*
Rare	Jaundice
Very rare	Hepatic failure, hepatitis
Skin and subcutaneous tissue disorders	
Uncommon	Rash papular, urticaria, hyperhidrosis, *pruritus*
Rare	*Stevens Johnson syndrome,* cold sweat, *Toxic epidermal necrolysis*
Musculoskeletal and connective tissue disorders	
Common	Muscle cramp, arthralgia, back pain, pain in limb, cervical spasm
Uncommon	Joint swelling, myalgia, muscle twitching, neck pain, muscle stiffness
Rare	Rhabdomyolysis
Renal and urinary disorders	
Uncommon	Urinary incontinence, dysuria
Rare	Renal failure, oliguria, *urinary retention*
Reproductive system and breast disorders	
Common	Erectile dysfunction
Uncommon	Sexual dysfunction, ejaculation delayed, dysmenorrhoea, breast pain
Rare	Amenorrhoea, breast discharge, breast enlargement, *gynaecomastia*
General disorders and administration site conditions	
Common	Oedema peripheral, oedema, gait abnormal, fall, feeling drunk, feeling abnormal, fatigue
Uncommon	Generalised oedema, *face oedema*, chest tightness, pain, pyrexia, thirst, chills, asthenia
Investigations	
Common	Weight increased
Uncommon	Blood creatine phosphokinase increased, blood glucose increased, platelet count decreased, blood creatinine increased, blood potassium decreased, weight decreased
Rare	White blood cell count decreased

* Alanine aminotransferase increased (ALT) and aspartate aminotransferase increased (AST).

After discontinuation of short-term and long-term treatment with pregabalin, withdrawal symptoms have been observed in some patients. The following reactions have been mentioned: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, convulsions, nervousness, depression, pain, hyperhidrosis, and dizziness, suggestive of physical dependence. The patient should be informed about this at the start of the treatment.
Concerning discontinuation of long-term treatment of pregabalin data suggest that the incidence and severity of withdrawal symptoms may be dose-related.
Paediatric population
The pregabalin safety profile observed in five paediatric studies in patients with partial seizures with or without secondary generalisation (12-week efficacy and safety study in patients 4 to 16 years of age, n=295; 14-day efficacy and safety study in patients 1 month to younger than 4 years of age, n=175; pharmacokinetic and tolerability study, n=65; and two 1 year open label follow on safety studies, n=54 and n=431) was similar to that observed in the adult studies of patients with epilepsy. The most common adverse events observed in the 12-week study with pregabalin treatment were somnolence, pyrexia, upper respiratory tract infection, increased appetite, weight increased, and nasopharyngitis. The most common adverse events observed in the 14-day study with pregabalin treatment were somnolence, upper respiratory tract infection, and pyrexia (see sections 4.2, 5.2 and 5.3).
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.

4.9 Overdose
In the postmarketing experience, the most commonly reported adverse reactions observed when pregabalin was taken in overdose included somnolence, confusional state, agitation, and restlessness. Seizures were also reported.
In rare occasions, cases of coma have been reported.
Treatment of pregabalin overdose should include general supportive measures and may include haemodialysis if necessary (see section 4.2, Table 1).

5 PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of action
Pregabalin binds to an auxiliary subunit (α2-δ protein) of voltage-gated calcium channels in the central nervous system.

5.2 Pharmacodynamic properties
Pharmacotherapeutic group: Anti-epileptics, other anti-epileptics ATC code: N03AX16
The active substance, pregabalin, is a gamma-aminobutyric acid analogue [(S)-3-(aminomethyl)-5-methylhexanoic acid].
Clinical efficacy and safety
Neuropathic pain
Efficacy has been shown in trials in diabetic neuropathy, post-herpetic neuralgia and spinal cord injury. Efficacy has not been studied in other models of neuropathic pain.
Pregabalin has been studied in 10 controlled clinical trials of up to 13 weeks with twice a day dosing (BID) and up to 8 weeks with three times a day (TID) dosing. Overall, the safety and efficacy profiles for BID and TID dosing regimens were similar.
In clinical trials up to 12 weeks for both peripheral and central neuropathic pain, a reduction in pain was seen by Week 1 and was maintained throughout the treatment period.
In controlled clinical trials in peripheral neuropathic pain 35% of the pregabalin-treated patients and 18% of the patients on placebo had a 50% improvement in pain score. For patients not experiencing somnolence, such an improvement was observed in 33% of patients treated with pregabalin and 18% of patients on placebo. For patients who experienced somnolence the responder rates were 48% on pregabalin and 16% on placebo.
In the controlled clinical trial in central neuropathic pain, 22% of the pregabalin treated patients and 7% of the patients on placebo had a 50% improvement in pain score.
Fibromyalgia
Pregabalin as monotherapy has been studied in 5 placebo-controlled studies, three of 12 weeks fixed-dose duration, one of 7 weeks fixed-dose duration and a 6-month study demonstrating long-term efficacy. Pregabalin treatment in all fixed-dose studies produced a significant reduction in pain associated with fibromyalgia at doses from 300 to 600 mg/day (BID).
In the three 12-week fixed -dose studies, 40% of pregabalin-treated patients experienced a 30% or more improvement in pain score versus 28% of the patients on placebo; 23% of treated patients experienced a 50% or more improvement in pain score versus 15% of the patients on placebo.
Pregabalin produced significantly superior global assessment scores via the Patient Global Impression of Change (PGIC) in the three 12-week fixed dose studies as compared to placebo treatment (41% patients feeling very much or much improved on pregabalin versus 29% on placebo).
As measured by Fibromyalgia Impact Questionnaire (FIQ), pregabalin produced a statistically significant improvement in function versus placebo treatment in 2 out of the 3 fixed-dose studies in which it was evaluated.
Pregabalin treatment produced significant improvements in patient-reported sleep outcomes in the 4 fixed-dose studies as measured by MOS-SS Sleep disturbance subscale (Medical Outcomes Study Sleep Scale), MOS-SS overall sleep problem index, and the daily sleep quality diary.
In the 6-month study, improvement in pain, global assessment (PGIC), function (FIQ total score) and sleep (MOS-SS Sleep disturbance subscale) were maintained for pregabalin-treated patients for a significantly longer period compared to placebo.
Pregabalin 600 mg/day showed an additional improvement in patient-reported sleep outcomes as compared to 300 and 450 mg/day; mean effects on pain, global assessment, and FIQ were similar at 450 and 600 mg/day, although the 600 mg/day dose was less well tolerated.

5.3 Pharmacokinetic properties
Pregabalin steady-state pharmacokinetics are similar in healthy volunteers and patients with chronic pain.
Absorption
Pregabalin is rapidly absorbed when administered in the fasted state, with peak plasma concentrations occurring within 1 hour following both single and multiple dose administration. Pregabalin oral bioavailability is estimated to be ≥90% and is independent of dose. Following repeated administration, steady-state is achieved within 24 to 48 hours. The rate of pregabalin absorption is decreased when given with food resulting in a decrease in C_{max} by approximately 25-30% and a delay in t_{max} to approximately 2.5 hours. However, administration of pregabalin with food has no clinically significant effect on the extent of pregabalin absorption.
Distribution
In preclinical studies, pregabalin has been shown to cross the blood brain barrier in mice, rats, and monkeys. Pregabalin has been shown to cross the placenta in rats and is present in the milk of lactating rats. In humans, the apparent volume of distribution of pregabalin following oral administration is approximately 0.56 l/kg. Pregabalin is not bound to plasma proteins.
Biotransformation
Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabelled pregabalin, approximately 98% of the radioactivity recovered in the urine was unchanged pregabalin. The N-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0.9% of the dose. In preclinical studies, there was no indication of racemisation of pregabalin S-enantiomer to the R-enantiomer.
Elimination
Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. Pregabalin mean elimination half-life is 6.3 hours. Pregabalin plasma clearance and renal clearance are directly proportional to creatinine clearance (see section 5.3 Renal impairment).
Dose adjustment in patients with reduced renal function or undergoing haemodialysis is necessary (see section 4.2, Table 1).
Linearity/non-linearity
Pregabalin pharmacokinetics are linear over the recommended daily dose range. Inter-subject pharmacokinetic variability for pregabalin is low (<20%). Multiple-dose pharmacokinetics are predictable from single-dose data. Therefore, there is no need for routine monitoring of plasma concentrations of pregabalin.
Gender
Clinical trials indicate that gender does not have a clinically significant influence on the plasma concentrations of pregabalin.
Renal impairment
Pregabalin clearance is directly proportional to creatinine clearance. In addition, pregabalin is effectively removed from plasma by haemodialysis (following a 4 hour haemodialysis treatment plasma pregabalin concentrations are reduced by approximately 50%). Because renal elimination is the major elimination pathway, dose reduction in patients with renal impairment and dose supplementation following haemodialysis is necessary (see section 4.2, 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.
Paediatric population
Pregabalin pharmacokinetics were evaluated in paediatric patients with epilepsy (age groups: 1 to 23 months, 2 to 6 years, 7 to 11 years and 12 to 16 years) at dose levels of 2.5, 5, 10 and 15 mg/kg/day in a pharmacokinetic and tolerability study.
After oral administration of pregabalin in paediatric patients in the fasted state, in general, time to reach peak plasma concentration was similar across the entire age group and occurred 0.5 hours to 2 hours postdose.
Pregabalin C_{max} and AUC parameters increased in a linear manner with increasing dose within each age group. The AUC was lower by 30% in paediatric patients below a weight of 30 kg due to an increased body weight adjusted clearance of 43% for these patients in comparison to patients weighing ≥30 kg.
Pregabalin terminal half-life averaged about 3 to 4 hours in paediatric patients up to 6 years of age, and 4 to 6 hours in those 7 years of age and older.
Population pharmacokinetic analysis showed that creatinine clearance was a significant covariate of pregabalin oral clearance, body weight was a significant covariate of pregabalin apparent oral volume of distribution, and these relationships were similar in paediatric and adult patients.
Pregabalin pharmacokinetics in patients younger than 3 months old have not been studied (see sections 4.2, 4.8 and 5.2).
Elderly
Pregabalin clearance tends to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with decreases in creatinine clearance associated with increasing age. Reduction of pregabalin dose may be required in patients who have age-related compromised renal function (see section 4.2, Table 1).
Breast-feeding mothers
The pharmacokinetics of 150 mg pregabalin given every 12 hours (300 mg daily dose) was evaluated in 10 lactating women who were at least 12 weeks postpartum. Lactation had little to no influence on pregabalin pharmacokinetics. Pregabalin was excreted into breast milk with average steady-state concentrations approximately 76% of those in maternal plasma. The estimated infant dose from breast milk (assuming mean milk consumption of 150 mL/kg/day) of women receiving 300 mg/day or the maximum dose of 600 mg/day would be 0.31 or 0.62 mg/kg/day, respectively. These estimated doses are approximately 7% of the total daily maternal dose on a mg/kg basis.

6 NONCLINICAL PROPERTIES

6.1 Animal toxicology or pharmacology
In conventional safety pharmacology studies in animals, pregabalin was well-tolerated at clinically relevant doses. In repeated dose toxicity studies in rats and monkeys CNS effects were observed, including hypoactivity, hyperactivity and ataxia. An increased incidence of retinal atrophy commonly observed in aged albino rats was seen after long-term exposure to pregabalin at exposures ≥5 times the mean human exposure at the maximum recommended clinical dose.
Pregabalin was not teratogenic in mice, rats or rabbits. Foetal toxicity in rats and rabbits occurred only at exposures sufficiently above human exposure. In prenatal/postnatal toxicity studies, pregabalin induced offspring developmental toxicity in rats at exposures >2 times the maximum recommended human exposure.
Adverse effects on fertility in male and female rats were only observed at exposures sufficiently in excess of therapeutic exposure. Adverse effects on male reproductive organs and sperm parameters were reversible and occurred only at exposures sufficiently in excess of therapeutic exposure or were associated with spontaneous degenerative processes in male reproductive organs in the rat. Therefore the effects were considered of little or no clinical relevance.
Pregabalin is not genotoxic based on results of a battery of *in vitro* and *in vivo* tests.
Two-year carcinogenicity studies with pregabalin were conducted in rats and mice. No tumours were observed in rats at exposures up to 24 times the mean human exposure at the maximum recommended clinical dose of 600 mg/day. In mice, no increased incidence of tumours was found at exposures similar to the mean human exposure, but an increased incidence of haemangiosarcoma was observed at higher exposures. The non-genotoxic mechanism of pregabalin-induced tumour formation in mice involves platelet changes and associated endothelial cell proliferation. These platelet changes were not present in rats or in humans based on short-term and limited long-term clinical data. There is no evidence to suggest an associated risk to humans.
In juvenile rats the types of toxicity do not differ qualitatively from those observed in adult rats. However, juvenile rats are more sensitive. At therapeutic exposures, there was evidence of CNS clinical signs of hyperactivity and bruxism and some changes in growth (transient body weight gain suppression). Effects on the oestrus cycle were observed at 5-fold the human therapeutic exposure. Reduced acoustic startle response was observed in juvenile rats 1-2 weeks after exposure at >2 times the human therapeutic exposure. Nine weeks after exposure, this effect was no longer observable.

7 DESCRIPTION
Pregabalin drug product is supplied as opaque hard gelatin shell capsules; the capsules imprinted with black ink to indicate the strength and product code.
Pregabalin 25 mg hard gelatin capsules
White marked “Pfizer” on the cap and “PGN 25” on the body with black ink
Pregabalin 50 mg hard gelatin capsules
White marked “Pfizer” on the cap and “PGN 50” on the body with black ink. The body is also marked with a black band
Pregabalin 75 mg hard gelatin capsules
White and orange, marked “Pfizer” on the cap and “PGN 75” on the body with black ink.
Pregabalin Pfizer 150 mg hard gelatin capsules
White marked “Pfizer” on the cap and “PGN 150” on the body with black ink.

8 PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities
Not applicable.

8.2 Shelf-life
3 years

8.3 Packaging information
For 25 mg, 50 mg, 75 mg and 150 mg:
14 Capsules per blister pack of clear PVC; one blister per carton.

8.4 Storage and handling instructions
Store protected from moisture, at a temperature not exceeding 30°C.
Instructions for handling
No special requirements.

9 PATIENT COUNSELLING INFORMATION
Angioedema
Advise patients that Pregabalin may cause angioedema, with swelling of the face, mouth (lip, gum, tongue) and neck (larynx and pharynx) that can lead to life-threatening respiratory compromise. Instruct patients to discontinue Pregabalin and immediately seek medical care if they experience these symptoms (see section 4.4).
Hypersensitivity
Advise patients that Pregabalin has been associated with hypersensitivity reactions such as wheezing, dyspnoea, rash, hives, and blisters. Instruct patients to discontinue Pregabalin and immediately seek medical care if they experience these symptoms (see section 4.4).
Suicidal Thinking and Behaviour
Patients, their caregivers, and families should be counselled that AEDs, including Pregabalin, may increase the risk of suicidal thoughts and behaviour and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behaviour, or the emergence of suicidal thoughts, behaviour, or thoughts about self-harm. Report behaviours of concern immediately to healthcare providers (see section 4.4).
Respiratory Depression
Inform patients about the risk of respiratory depression. Include information that the risk is greatest for those using concomitant central nervous system (CNS) depressants (such as opioid analgesics) or in those with underlying respiratory impairment. Teach patients how to recognize respiratory depression and advise them to seek medical attention immediately if it occurs (see section 4.4).
Dizziness and Somnolence
Counsel patients that Pregabalin may cause dizziness, somnolence, blurred vision and other CNS signs and symptoms. Accordingly, advise patients not to drive, operate complex machinery, or engage in other hazardous activities until they have gained sufficient experience on Pregabalin to gauge whether or not it affects their mental, visual, and/or motor performance adversely (see section 4.4).
CNS Depressants
Inform patients who require concomitant treatment with central nervous system depressants such as opiates or benzodiazepines that they may experience additive CNS side effects, such as respiratory depression, somnolence, and dizziness (see section 4.4 and 4.6). Advise patients to avoid consuming alcohol while taking Pregabalin, as it may potentiate the impairment of motor skills and sedating effects of alcohol.
Adverse Reactions with Abrupt or Rapid Discontinuation
Advise patients to take Pregabalin prescribed. Abrupt or rapid discontinuation may result in increased seizure frequency in patients with seizure disorders, and insomnia, nausea, headache, anxiety, hyperhidrosis, or diarrhea (see section 4.4).
Missed Dose
Counsel patients if they miss a dose, they should take it as soon as they remember. If it is almost time for the next dose, they should skip the missed dose and take the next dose at their regularly scheduled time. Instruct patients not to take two doses at the same time.
Weight Gain and Edema
Counsel patients that Pregabalin may cause edema and weight gain. Advise patients that concomitant treatment with Pregabalin and a thiazolidinedione antidiabetic agent may lead to an additive effect on edema and weight gain. For patients with preexisting cardiac conditions, this may increase the risk of heart failure (see section 4.4 and 4.8).
Ophthalmological Effects
Counsel patients that Pregabalin may cause visual disturbances. Inform patients that if changes in vision occur, they should notify their physician (see section 4.4).
Pregnancy
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Pregabalin during pregnancy (see section 4.6).
Lactation
Advise nursing mothers that breastfeeding is not recommended during treatment with Pregabalin (see section 4.6).

10. DETAILS OF MANUFACTURER
Manufactured by:
M/s. Pfizer Manufacturing Deutschland GmbH,
Betriebsstätte Freiburg, Mooswaldallee 1, 79090 Freiburg, Germany

Imported and marketed in India by:
Mylan Pharmaceuticals Private Limited
BLD No. 16, Room No.1 & 2,
Survey No. 99/1, Village Nimji,
Kalameshwar - 441501,
Nagpur, Maharashtra, India.

11 DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE
IL/FF-000649 - RC/FF-002310 Dated 19 May 2023 (The license is renewed every 3 years per regulations).

12 DATE OF REVISION
May 2023
For reporting of adverse events and PV related queries please write to
Email: ProductSafety@viatris.com

VIATRIS
3042833
PAA205681

VIATRIS

Description	Lyrica_75mg_150mg_14s_blister_PP LYRICA 75/150mg IN			**Date: 26 May 23**	**Time: 12:00**
Component Type	Leaflet	**Site Barcode/ DataMatrix**	2594	**No. of colours** 1	**Page Count** 2 of 2
Affiliate Item Code	3042833	**Viatris SAP No.**	400564412;400564413	**Colours**	Black
Superseded Affiliate Item Code	N/A	**Vendor Job No.**	108382258/0020	**Non-Print Colours**	Keyline
TrackWise/GLAMS Job No-	3042833	**Artwork Proof No.**	1		
MA No.	IL/FF-000649 - RC/FF-002310	**Client Market**	India	**Equate CMYK with**	
Packing Site/Printer	Pfizer Manufacturing Freiburg (Freiburg - DE)	**Keyline/Drawing No.**	003000009449_3_420x180mm_v1_FVID1328153		
New Supplier Code	PAA205681	**Barcode Info**	N/A	**Main Font**	Helvetica Neue LT W1G **Body Text Size** 6 pt
Superseded Supplier Code	PAA172484	**3D Render ID**	N/A	**Dimensions**	180 x 420 mm **Min Text Size used** 6 pt
Supplier SAP No.	N/A				
Sign-offs					
					V2 Oct 2022