INDOCO REMEDIES LTD.	Packaging Development Department

Item:	**Leaflet**
Item Code:	XXXXXXX
Open Size:	510 x 130 mm
Folding Size:	H:Unfolded: 510 mm Folded:32 mm
	W:Unfolded:130mm Folded: 120mm
GSM/ Paper:	40 gsm Bible paper
Colour:	Black
Pharmacode:	Front:

Reason for Preparation/ Revision:

1) New Development

Prepared by	Checked by	Approved by

Path	Z:\P\Pregabalin Capsules\Unimed\Current 23\Pregabalin Leaflet 360 x 120 mm XXXXXXX.cdr	R1

Date: 27.10.2020/ 07.11.22/ 09.11.22 / 09.12.2022/ 23.01.23/ 31.03.23/ 07.04.23/ 09.06.23/ 03.08.23 / 05.01.24 / 09.01.24

130 mm | 6 mm | 10 mm | 6 mm | 130 mm

510 mm

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

PGB-75

Pregabalin 75 mg Capsules

COMPOSITION

Pregabalin 75 mg capsules

Each hard gelatin capsule contains:

Pregabalin……75mg

Also contains Titanium dioxide, Red Iron Oxide

PRODUCT DESCRIPTION

Pregabalin 75 mg Capsules

White and Orange hard gelatin capsules of size "4" with "I" printed on cap and "35" on body containing white to off white powder.

Dosage Form: Hard gelatine capsules (Capsule)

CLINICAL PHARMACOLOGY

Pharmacodynamics

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

Mechanism of action

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

Pharmacokinetics

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

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

Distribution In preclinical studies, pregabalin has been shown to cross the blood brain barrier in mice, rats, and monkeys. Pregabalin has been shown to cross the placenta in rats and is present in the milk of lactating rats. In humans, the apparent volume of distribution of pregabalin following oral administration is approximately 0.56 l/kg. Pregabalin is not bound to plasma proteins.

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.

Dose adjustment in patients with reduced renal function or undergoing haemodialysis is necessary

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.

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

Pregabalin clearance tends to decrease with increasing age. Reduction of pregabalin dose may be required in patients who have age related compromised renal function.

INDICATIONS

Neuropathic pain

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

Epilepsy

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

Generalised anxiety disorder

Pregabalin is indicated for the treatment of Generalised Anxiety Disorder (GAD) in adults.

Fibromyalgia

Pregabalin is indicated for the treatment of Fibromyalgia.

DOSAGE AND ADMINISTRATION

Recommended Dose

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

Pregabalin may be taken with or without food.

Neuropathic pain

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

Fibromyalgia

The usual dose range for most patients is 300 to 450 mg per day given in two divided doses. Some patients may derive additional benefit at 600 mg per day. Dosing should begin at 75 mg two times a day (150 mg/day) and may be increased to 150 mg two times a day (300 mg/day) within 1 week based on efficacy and tolerability. Patients who do not experience sufficient benefit with 300 mg/day may be further increased to 225 mg two times a day (450 mg/day). If needed, in some patients, based on individual response and tolerability, the dose may be increased to maximum dosage of 600 mg/day after an additional week.

Epilepsy

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

Generalised anxiety disorder

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

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

Discontinuation of pregabalin

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

Pharma Code

7 mm | 16 mm | 7 mm

Patients with renal impairment

Dosage reduction in patients with compromised renal function must be individualized according to creatinine clearance (Clcr), as indicated in Table 1 determined using the following formula:

$$\text{CLcr(ml/min)} = \frac{[\{140 - \text{age (years)}\} \times \text{weight (kg)}]}{72 \times \text{Serum creatinine (mg/dL)}} \quad (\times 0.85 \text{ for female patients})$$

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

Table 1. Pregabalin Dose Adjustment Based on Renal Function

	Total Pregabalin Daily Dose*		
Creatinine clearance (CLcr) (ml/min)	Starting dose (mg/day)	Maximum dose (mg/day)	Dose regimen
≥ 60	150	600	BID or TID
≥ 30 - < 60	75	300	BID or TID
≥ 15 - < 30	25 – 50	150	QD or BID
< 15	25	75	QD
Supplementary dosage following haemodialysis (mg)			
	25	100	Single dose+

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

Use in patients with hepatic impairment

No dosage adjustment is required for patients with hepatic impairment

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

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

The use in children is not recommended.

Use in the elderly (over 65 years of age)

Elderly patients may require a dose reduction of pregabalin due to a decreased renal function.

Route of Administration: Oral

ADVERSE EFFECTS

The most commonly reported adverse reactions were dizziness and somnolence. Adverse reactions were usually mild to moderate in intensity.

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).

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.

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

Table 2. Pregabalin Adverse Drug Reactions

System Organ Class	Adverse drug reactions
Infections and infestations	
Common	Nasopharyngitis
Metabolism and nutrition disorders	
Common	Appetite increased
Uncommon	Anorexia, hypoglycaemia
Psychiatric disorders	
Common	Euphoric mood, confusion, irritability, disorientation, insomnia, libido decreased
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
Eye disorders	
Common	Vision blurred, diplopia
Uncommon	Peripheral vision loss, visual distuebance, eye swelling, visual field defect, visual acuity reduced, eye pain, asthehopia, photopsia, dry eye, lacrimation increased, eye irritation.
Ear and labyrinth disorders	
Common	Vertigo
Uncommon	Hyperacusis
Cardiac disorders	
Uncommon	Tachycardia, atrioventricular block first degree, sinus bradycardia, congestive heart failure
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, epistaxis, cough, nasal oongestion, rhinitis, snoring, nasal dryness
Gastroin test in all disorders	
Common	Vomiting, nausea, constipation, diarrhoea, flatulence, abdominal distension, dry mouth
Uncommon	Gastrooes ophageal reflux disease, salivary hyper secretion, hypoaesthesia oral.
Musculoskeletal and connective tissue disorders	
Common	Muscle cramp, arthralgia, back pain, pain in limb, cervical spasm
Reproductive system and breast disorders	
Common	Erectile dysfunction
Uncommon	Sexual dysfunction, ejaculation delayed, dysmenorrhoea, breast pain
General disorders and administration site conditions	
Common	Oedema peripheral, oedema, gait abnormal, fall, feeling drunk, feeling abnormal fatigue.
Investigations	
Common	Weight increased
Uncommon	Blood creatine phosphokinase increased, blood glucose increased, platelet count decreased, blood creatinine increased, blood potassium decreased, weight decreased.

CONTRAINDICATIONS

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

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Potential for an increase in risk of suicidal thoughts or behaviors.

Angioedema

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

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

Hypersensitivity

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

Suicidal Behavior and Ideation

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

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

Respiratory Depression

There is evidence from case reports, human studies, and animal studies associating pregabalin with serious, life-threatening, or fatal respiratory depression when co-administered with central nervous system (CNS) depressants, including opioids, or in the setting of underlying respiratory impairment. When the decision is made to co-prescribe pregabalin with another CNS depressant, particularly an opioid, or to prescribe pregabalin to patients with underlying respiratory impairment, monitor patients for symptoms of respiratory depression and sedation, and consider initiating pregabalin at a low dose. The management of respiratory depression may include close observation, supportive measures, and reduction or withdrawal of CNS depressants (including pregabalin).

Dizziness and Somnolence

Pregabalin may cause dizziness and somnolence. Inform patients that pregabalin-related dizziness and somnolence may impair their ability to perform tasks such as driving or operating machinery and could increase the occurrence of accidental injury (fall) in the elderly population.

Pregabalin is not known to be active at receptor sites associated with drugs of abuse. Cases of misuse and abuse have been reported in the post-marketing database. As with any CNS active drug, carefully evaluate patients for history of drug abuse and observe them for signs of pregabalin misuse or abuse (e.g., development of tolerance, dose escalation, drug-seeking behavior).

Increased Risk of Adverse Reactions with Abrupt or Rapid Discontinuation

As with all antiepileptic drugs (AEDs), withdraw pregabalin gradually to minimize the potential of increased seizure frequency in patients with seizure disorders. Following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache, anxiety, hyperhidrosis, and diarrhea.

Peripheral Edema

Pregabalin treatment may cause peripheral edema. In short-term trials of patients without clinically significant heart or peripheral vascular disease, there was no apparent association between peripheral edema and cardiovascular complications such as hypertension or congestive heart failure. Peripheral edema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function.

As the thiazolidinedione class of antidiabetic drugs can cause weight gain and/or fluid retention, possibly exacerbating or leading to heart failure, exercise caution when co-administering pregabalin and these agents.

Weight Gain

Pregabalin treatment may cause weight gain. In pregabalin controlled clinical trials in adult patients of up to 14 weeks, a gain of 7% or more over baseline weight was observed in 9% of pregabalin-treated patients and 2% of placebo-treated patients. Few patients treated with pregabalin (0.3%) withdrew from controlled trials due to weight gain. Pregabalin associated weight gain was related to dose and duration of exposure, but did not appear to be associated with baseline BMI, gender, or age. Weight gain was not limited to patients with edema (see Section 4.4 Special warnings and precautions for use).

Although weight gain was not associated with clinically important changes in blood pressure in shortterm controlled studies, the long-term cardiovascular effects of pregabalin-associated weight gain are unknown.

Among diabetic patients, pregabalin-treated patients gained an average of 1.6 kg (range: -16 to 16 kg), compared to an average 0.3 kg (range: -10 to 9 kg) weight gain in placebo patients. In a cohort of 333 diabetic patients who received pregabalin for at least 2 years, the average weight gain was 5.2 kg. While the effects of pregabalin-associated weight gain on glycemic control have not been systematically assessed, in controlled and longer-term open label clinical trials with diabetic patients, pregabalin treatment did not appear to be associated with loss of glycemic control (as measured by HbA1C). Some diabetic patients who gain weight on pregabalin treatment may need to adjust hypoglycemic medications.

Abrupt or Rapid Discontinuation

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

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

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

Tumorigenic Potential

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

Ophthalmological Effects

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

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

Creatine Kinase Elevations

Pregabalin treatment was associated with creatine kinase elevations. Mean changes in creatine kinase from baseline to the maximum value were 60 U/L for pregabalin-treated patients and 28 U/L for the placebo patients.

Instruct patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if these muscle symptoms are accompanied by malaise or fever. Discontinue treatment with pregabalin if myopathy is diagnosed or suspected or if markedly elevated creatine kinase levels occur.

Decreased Platelet Count

Pregabalin treatment was associated with a decrease in platelet count. Pregabalin-treated subjects experienced a mean maximal decrease in platelet count of 20 × 103 /µL, compared to 11 × 103 /µL in placebo patients.

PR Interval Prolongation

Pregabalin treatment was associated with PR interval prolongation.

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

Women of childbearing potential/Contraception

Pregabalin use in the first trimester of pregnancy may cause major birth defects in the unborn child. Pregabalin should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the fetus. Women of childbearing potential must use effective contraception during treatment

Others

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

Misuse, abuse potential or dependence

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

Encephalopathy

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

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.

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.

DRUG 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 and coma in patients taking pregabalin and 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.

Pregnancy category C

There are no adequate data from the use of pregabalin in pregnant women.

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

Lactation

Pregabalin is excreted into human milk. 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 breast-feeding for the child and the benefit of therapy for the woman.

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

PRESENTATION : PVC/Aluminium blisters containing 14 hard gelatin capsules.

MANUFACTURED BY
INDOCO REMEDIES LTD.
Plant I, L-14, Verna Industrial Area, Verna, IN-403 722, India.

Revision Date: August 2023

Name and Address of
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