LEPTICA
Capsule

Compositions:
LEPTICA 75 MG
Each capsule contains
Pregabalin 75 mg

LEPTICA 150 MG
Each capsule contains
Pregabalin 150 mg

List of Excipients:
LEPTICA 75 MG
Spray dried lactose DCL 11, corn starch, talc, capsule shells Leptica 75 mg size 3 (cap scarlet and body white).

LEPTICA 150 MG
Spray dried lactose DCL 11, corn starch, talc, capsule shells Leptica 150 mg size 2 (body and cap white op. (44.700))

Product Descriptions:
LEPTICA 75 MG
Hard gelatin capsule, cap scarlet, body white, contain white crystalline powder. Cap printed DXM logo in black, body unmark.

LEPTICA 150 MG
Hard gelatin capsule, body and cap white op. (44.700), contain white crystalline powder. Cap printed DXM logo in black, body unmark.

Pharmacodynamics:
ATC code: N03AX16
Mechanism of action
Pregabalin binds to an auxiliary subunit (α2-δ protein) of voltage-gated calcium channels in the central nervous system.
Evidence from animal models with nerve damage has shown that pregabalin reduces calcium dependent release of pronociceptive neurotransmitters in the spinal cord possibly by disrupting calcium trafficking and/or reducing calcium currents. Evidence from other animal models of nerve damage suggests the antinociceptive activities of pregabalin may also be mediated through interactions with the descending noradrenergic and serotonergic pathways.

Clinical experience
Neuropathic pain
Efficacy has been shown in studies in diabetic neuropathy and postherpetic neuralgia. Efficacy has not been studied in other models of neuropathic pain. Pregabalin has been studied in 9 controlled clinical studies of up to 13 weeks with twice a day dosing and up to 8 weeks with three times a day dosing. Overall, the safety and efficacy profiles for twice a day and three times a day dosing regimens were similar.
In clinical trials up to 13 weeks, a reduction in pain was seen by week 1 and was maintained throughout the treatment period. In controlled clinical trials, 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.

Epilepsy
Pregabalin has been studied in 3 controlled clinical studies of 12-week duration with either twice a day dosing or three times a day dosing. Overall, the safety and efficacy profiles for twice a day and three times a day dosing regimens were similar. A reduction in seizure frequency was observed by week 1.

Generalized anxiety disorder
Pregabalin has been studied in 6 controlled studies of 4 to 6 weeks duration, an elderly study of 8 weeks duration and a long-term relapse prevention study with a double-blind relapse prevention phase of 6 months duration.
Relief of the symptoms of GAD as reflected by the Hamilton Anxiety Rating Scale (HAM-A) was observed by week 1.
In controlled clinical trials (4-8 weeks duration), 52% of the pregabalin-treated patients and 38% of the patients on placebo had at least a 50% improvement in HAM-A total score from baseline to endpoint.

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 months 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 per day (BID).

In the three 12 weeks 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 weeks 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 Medical Outcomes Study Sleep Scale (MOS-SS) Sleep disturbance subscale, MOS-SS overall sleep problem index, and the daily sleep quality diary.

In the 6 months 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 per day showed an additional improvement in patient-reported sleep outcomes as compared to 300 and 450 mg per day; mean effects on pain, global assessment, and FIQ were similar at 450 and 600 mg per day, although the 600 mg per day dose was less well tolerated.

Pharmacokinetics:
Pregabalin steady-state pharmacokinetics are similar in healthy patients, patients with epilepsy receiving antiepileptic 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
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.

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. There was no indication of racemization 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.

Dosage adjustment in patients with reduced renal function or undergoing hemodialysis is necessary.

Linearity/nonlinearity
Pregabalin pharmacokinetics are linear over the recommended daily dose range. Intersubject 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.

Pharmacokinetics in special patient groups
Gender
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 hemodialysis (following a 4-hour hemodialysis 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 hemodialysis is necessary.

Hepatic impairment
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 (over 65 years of age)
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.

Breastfeeding mothers
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 approximately 7% of the maternal dose.

Indications:
Neuropathic pain
Pregabalin is indicated for the treatment of neuropathic pain which includes diabetic peripheral neuropathy and postherpetic neuralgia in adults.

Epilepsy
Pregabalin is indicated as adjunctive therapy of partial seizures, with or without secondary generalization, in adults.

Generalized anxiety disorder
Pregabalin is indicated for the treatment of generalized anxiety disorder (GAD) in adults.

Fibromyalgia
Pregabalin is indicated for the management of fibromyalgia.

Recommended Dosage:
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.

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.

Generalized 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 dose may be increased to 300 mg per day after 1 week. Following an additional week the dose may be increased to 450 mg per day. The maximum dose of 600 mg per day may be achieved after an additional week.

Fibromyalgia
The recommended dose of pregabalin is 300 to 450 mg per day. Dosing should begin at 75 mg two times a day (150 mg per day) and may be increased to 150 mg two times a day (300 mg per day) within 1 week based on efficacy and tolerability. Patients who do not experience sufficient benefit with 300 mg per day may be further increased to 225 mg two times a day (450 mg per day). Although pregabalin was also studied at 600 mg per day, there is no evidence that this dose confers additional benefit and that this dose was less tolerated.

In view of the dose-dependent adverse reactions, treatment with doses above 450 mg per day is not recommended.

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

Patients with renal impairment
Dose reduction in patients with compromised renal function must be individualized according to creatinine clearance (Clcr), as indicated in table determined using the following formula:

$$\text{Clcr (ml/minute)} = \frac{[140\text{-age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}} \times (0.85 \text{ for female patients})$$

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 hemodialysis treatment (see table).

Pregabalin dose adjustment based on renal function

Creatinine clearance (Clcr) (ml/minute)	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	QD or BID
<15	25	75	QD
Supplementary dosage following hemodialysis (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.

Patients with hepatic impairment
No dose 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 in adolescents have not been established. The use in children and adolescents 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.

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

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

Some diabetic patients who gain weight on pregabalin treatment may need to adjust hypoglycemic medications.

There have been reports 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.

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 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 medication.

Transient visual blurring and other changes in visual acuity have been reported in patients treated with pregabalin. Discontinuation of pregabalin may result in resolution or improvement of these visual symptoms.

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

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, diarrhea, flu syndrome, nervousness, depression, pain, sweating, and dizziness. The patients should be informed about this at the start of the treatment.

Pregabalin is not known to be active at receptor sites associated with drugs of abuse. Cases of misuse and abuse have been reported. 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).

Concerning discontinuation of long-term treatment of pregabalin there are no data of the incidence and severity of withdrawal symptoms in relation to duration of use and dose of pregabalin.

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

There have been reports of congestive heart failure in some patients receiving pregabalin. In short-term use 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. Because there are limited data on severe congestive heart failure patients, pregabalin should be used with caution in these patients.

Treatment with pregabalin was associated with creatine kinase elevations. There have been reports of rhabdomyolysis in some patients receiving pregabalin. 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 in the context of symptoms of myopathy.

Suicidal ideation and behavior have been reported in patients treated with antiepileptic agents in several indications. 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 behaviors and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behavior emerge.

Teratogenicity
Pregabalin was not teratogenic in mice, rats, or rabbits. Fetal 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.

Effects on 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 medication affects their ability to perform these activities.

Interactions with Other Medicines and Other Forms of Interaction:
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.

Accordingly, in *in vivo*, 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.

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

Pregabalin may potentiate the effects of ethanol and lorazepam. Multiple oral doses of pregabalin coadministered 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.

There are reports of respiratory failure and coma in patients taking pregabalin and other CNS depressant medications. There are reports of events related to reduced lower gastrointestinal tract function (e.g., intestinal obstruction, paralytic ileus, constipation) when pregabalin was coadministered with medications that have the potential to produce constipation, such as opioid analgesics.

No specific pharmacodynamic interactions were found in elderly patients.

Use during Pregnancy and Lactation:
Pregnancy
There is a limited amount of data on the use of pregabalin in pregnant women. Data from an observational study, which included more than 2,700 pregnancies exposed to pregabalin based on routinely collected data from administrative and medical registers in Denmark, Finland, Norway, and Sweden, is as follows:
- *Major congenital malformations (MCM)*
  The risk of MCM among the pediatric 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)).
- *Birth and postnatal neurodevelopmental outcomes*
  There were no statistically significant findings for stillbirth, low birth weight, preterm birth, small for gestational age (SGA), low Apgar score at 5 minutes, and microcephaly. Adjusted prevalence ratios (aPRs, and 95% confidence intervals) results for the meta-analysis for stillbirth, low birth weight, preterm birth, SGA, low Apgar score at 5 minutes, and microcephaly for pregabalin-exposed compared to unexposed to antiepileptic drugs (AEDs) of 1.72 (1.02-2.91), 1.05 (0.91-1.21), 1.13 (0.99-1.29), 1.21 (1.01-1.44), 1.18 (0.95-1.48), and 1.09 (0.88-1.36) respectively.

In pediatric population exposed *in utero*, the study did not provide evidence of an increased risk for attention deficit hyperactivity disorder (ADHD), autism spectrum disorders (ASD), and intellectual disabilities (ID). In the meta-analysis of the neurodevelopmental outcomes (ADHD, ASD, and ID), results for ADHD, ASD, and ID for pregabalin-exposed compared to unexposed to AEDs were 1.32 (1.04-1.67), 1.00 (0.68-1.47), and 1.03 (0.80-1.32) respectively.

Studies in animals have shown reproductive toxicity. Pregabalin should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the fetus. Effective contraception must be used in women of childbearing potential.

Lactation
Pregabalin is excreted in the milk of lactating women. As the safety of pregabalin in infants is not known, breastfeeding is not recommended during treatment with pregabalin. A decision must be made whether to discontinue breastfeeding or to discontinue from pregabalin therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Adverse Effects:
The frequencies shown below were defined using the following criteria: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), and rare (<1/1,000). The adverse effects listed may also be associated with the underlying disease and/or concomitant medications.
- Infections and infestations
  Common: nasopharyngitis.
- Immune system disorders
  Uncommon: hypersensitivity.
  Rare: angioedema, allergic reaction.
- Blood and lymphatic system disorders
  Uncommon: neutropenia.
- Metabolism and nutrition disorders
  Common: appetite increased.
  Uncommon: anorexia, hypoglycemia.
- Psychiatric disorders
  Common: euphoric mood, confusion, irritability, depression, disorientation, insomnia, libido decreased.
  Uncommon: hallucination, restlessness, agitation, depressed mood, elevated mood, mood swings, depersonalization, abnormal dreams, word finding difficulty, libido increased, anorgasmia.
  Rare: panic attack, disinhibition, apathy.
- Nervous system disorders
  Very common: dizziness, somnolence, headache.
  Common: ataxia, coordination abnormal, tremor, dysarthria, amnesia, memory impairment, disturbance in attention, paresthesia, hypoesthesia, sedation, balance disorder, lethargy.
  Uncommon: syncope, myoclonus, psychomotor hyperactivity, dyskinesia, dizziness postural, intention tremor, nystagmus, cognitive disorder, speech disorder, hyporeflexia, hyperesthesia, burning sensation, loss of consciousness, mental impairment.
  Rare: stupor, parosmia, hypokinesia, ageusia, dysgraphia.
- 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, keratitis.
- Ear and labyrinth disorders
  Common: vertigo.
  Uncommon: hyperacusis.
- Cardiac disorders
  Uncommon: tachycardia, atrioventricular block first degree, sinus bradycardia.
  Rare: sinus tachycardia, sinus arrhythmia, congestive heart failure.
- Vascular disorders
  Uncommon: hypotension, hypertension, hot flushes, flushing, peripheral coldness.
- Respiratory, thoracic, and mediastinal disorders
  Uncommon: dyspnea, epistaxis, cough, nasal congestion, rhinitis, snoring.
  Rare: throat tightness, nasal dryness, pulmonary edema.
- Gastrointestinal disorders
  Common: vomiting, constipation, flatulence, abdominal distension, dry mouth, nausea, diarrhea.
  Uncommon: gastroesophageal reflux disease, salivary hypersecretion, hypoesthesia oral.
  Rare: ascites, pancreatitis, dysphagia, swollen tongue.
- Skin and subcutaneous tissue disorders
  Uncommon: rash popular, urticaria, sweating, face swelling, pruritus.
  Rare: cold sweat, Stevens-Johnson syndrome.
- 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
  Uncommon: erectile dysfunction, sexual dysfunction, ejaculation delayed, dysmenorrhea.
  Rare: breast pain, amenorrhea, breast discharge, breast enlargement, gynecomastia.
- General disorders and administration site conditions
  Common: edema peripheral, edema, gait abnormal, fall, feeling drunk, felling abnormal, fatigue.
  Uncommon: generalized edema, chest tightness, pain, pyrexia, thirst, chills, asthenia, malaise.
- Investigations
  Common: weight increased.
  Uncommon: blood creatinine 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 creatinine increased.

Overdose and Treatment:
In overdose up to 15 g, no unexpected adverse reactions were reported. The most commonly reported adverse events observed when pregabalin was taken in overdose included affective disorder, somnolence, confusion state, depression, agitation, and restlessness. Seizures were also reported.
Treatment of pregabalin overdose should include general supportive measures and may include hemodialysis if necessary.

Presentations and Registration Numbers:
LEPTICA 75 MG: Box, 3 PVC rigid film/aluminium blisters x 10 capsules; SIN16076P
LEPTICA 150 MG: Box, 3 PVC rigid film/aluminium blisters x 10 capsules; SIN16075P

ON MEDICAL PRESCRIPTION ONLY.

STORE AT TEMPERATURES BELOW 30°C.

Manufactured by
PT Dexa Medica
Jl. Jend. Bambang Utoyo No. 138
Palembang-Indonesia

Date of Review: 25 August 2022

Fiber direction