SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

LEPTICA 150 mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 150 mg of pregabalin

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule

4. CLINICAL PARTICULARS

4.1. Therapeutic 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 generalization.
- Generalized anxiety disorder
  Pregabalin is indicated for the treatment of Generalized Anxiety Disorder (GAD) in adults.

4.2. Posology and method of administration

Dosage

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-days interval.
- Epilepsy
  Pregabalin treatment can be started with 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 1 week. The maximum dose of 600 mg per day may be achieved after an additional week.
- Generalized Anxiety Disorder (GAD)
  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.

- 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.

- Patients with 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, dose reduction in patients with compromised renal function must be i ndividualized according to creatinine clearance (Clcr), as indicated in table determined using the following formula:

$$Clcr\ (mL/minute) = \left[\frac{1.23\ x\ [140 - age\ (years)]\ x\ weight\ (kg)}{72\ x\ serum\ creatinine\ (mg/dL)}\right] (x\ 0.85\ for\ female\ patients)$$

Pregabalin is removed effectively from plasma by hemodialysis (50% of drug in 4 hours). 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-hours hemodialysis treatment (see table).

Table. **Pregabalin dose adjustment based on renal function**

Creatinine clearance (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	Once daily or BID
<15	25	75	Once daily
Supplementary dosage following hemodialysis (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.

- Patients with hepatic impairment

No dose adjustment is required for patients with hepatic impairment.

- Pediatric 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.

- Elderly population

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

Administration

LEPTICA is for oral use only. LEPTICA may be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients

4.4 Special warnings and precautions for use

Diabeticpatients

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

Hypersensitivityreactions

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.

Dizziness,somnolence,lossofconsciousness,confusion,andmentalimpairment

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.

Vision-relatedeffects

Visual adverse reactions have 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.

Renalfailure

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

Withdrawalofconcomitantantiepilepticmedications

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

Withdrawalsymptoms

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, diarrhea, flu syndrome, nervousness, depression, pain, convulsion, hyperhidrosis and dizziness, suggestive of physical dependence. The patients 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, the incidence and severity of withdrawal symptoms may be dose-related.

Congestiveheartfailure

There have been 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.

Treatmentofcentralneuropathicpainduetospinalcordinjury

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 medications (e.g. antispasticity agents) needed for this condition. This should be considered when prescribing pregabalin in this condition.

Suicidalideationandbehavior

Suicidal ideation and behavior have been reported in patients treated with antiepileptic agents in several indications. 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.

Reducedlowergastrointestinaltractfunction

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

Misuse,abusepotentialordependence

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 behavior have been reported).

Encephalopathy

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

Lactoseintolerance

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

4.5 Interaction with other medicinal products and other forms of interaction

Since pregabalin is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (<2% of a dose recovered in urine as metabolites), does not

inhibit drug metabolism, and is not bound to plasma proteins, it is unlikely to produce, or be subject to, pharmacokinetic interactions.

No clinically relevant pharmacokinetic interactions were observed between pregabalin and phenytoin, carbamazepine, valproic acid, lamotrigine, gabapentin, lorazepam, oxycodone or ethanol. Oral antidiabetics, diuretics, insulin, phenobarbital, tiagabine and topiramate had no clinically significant effect on pregabalin clearance.

Oralcontraceptives,norethisteroneand/orethinylestradiol

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

Centralnervoussysteminfluencingmedicinalproducts

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. There are reports of respiratory failure and coma in patients taking pregabalin and other central nervous system (CNS) depressant medications. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone.

Interactionsandtheelderly

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

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of pregabalin in pregnant women. The potential risk for humans is unknown. Pregabalin should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the fetus).

Breast-feeding

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.

Womenofchildbearingpotential

As the potential risk for human is unknown, effective contraception must be used in women of childbearing potential.

Fertility

There are no reports on the effects of pregabalin on female fertility.

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 medication affects their ability to perform these activities.

4.8 Undesirable effects

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

- Infections
  Common : nasopharyngitis.

- Blood and lymphatic system disorders. Uncommon
  : neutropenia.

- Immune system disorders
  Uncommon : hypersensitivity.
  Rare : angioedema, allergicreaction.

- Metabolism and nutrition disorders
  Common : appetite increased.
  Uncommon : anorexia, hypoglycemia.

- 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, depersonalization, 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, hypoesthesia, 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, hyperesthesia, burning sensation, ageusia, malaise.

  Rare : convulsions, parosmia, hypokinesia, dysgraphia.

- Eye disorders

  Common : blurred vision, 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.

- Vascular disorders

Uncommon : hypotension, hypertension, hot flushes, flushing, peripheral coldness.

- Respiratory, thoracic and mediastinal disorders

Uncommon : dyspnea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness.

Rare : pulmonary edema, throat tightness.

- Gastrointestinal disorders

Common : vomiting, nausea, constipation, diarrhea, flatulence, abdominal distenstion, dry mouth.

Uncommon : gastroesophageal reflux disease, salivary hypersecretion, hypoesthesia oral.

Rare : ascites, pancreatitis, swollen tongue, dysphagia.

- Hepatobilliary disorders

Uncommon : elevated alanine aminotransferase (ALT) and aspartate aminotransferase increased (AST).

Rare : jaundice.

Very rare : hepatic failure, hepatitis.

- Skin and subcutaneous tissue disorders

Uncommon : rash papular, urticaria, hyperhidrosis, pruritus. Rare : Stevens Johnson syndrome, cold sweat.

- 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, dysmenorrhea, breast pain. Rare : amenorrhea, breast discharge, breast enlargement, gynecomastia.

- General disorders and administration site conditions

Common : edema peripheral, edema, gait abnormal, fall, feeling drunk, feeling abnormal, fatigue.

Uncommon : generalized edema, face edema, 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.

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, diarrhea, 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, the incidence and severity of withdrawal symptoms may be dose-related.

The most common adverse events of pregabalin in pediatric population were somnolence, pyrexia, upper respiratory tract infection, increased appetite, weight increased and nasopharyngitis.

4.9 Overdose

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 hemodialysis if necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties Pharmacotherapeutic group*:* Other antiepileptics

ATC code:
N03AX16

Mechanism of action and pharmacodynamic effects
Pregabalin binds with high affinity to an auxiliary subunit (alpha$_2$-delta protein) of voltagegated calcium channels in the central nervous system.

5.2. Pharmacokinetic properties

Absorption

Pregabalin is rapidly absorbed when administered in the fasted state, with peak plasma concentrations occurring within 1 hour following both single and multiple dose administration. Pregabalin oral bioavailability is estimated to be ≥90% and dose independent. 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. The apparent volume of distribution of pregabalin following oral administration is approximately 0.56 liter/kg. Pregabalin is not bound to plasma proteins.

Biotransformation

Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabeled pregabalin, approximately 98% of the radioactivity recovered in the urine was unchanged. 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 Senantiomer 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.
Dose adjustment in patients with reduced renal function or undergoing hemodialysis is necessary.

Pregabalin pharmacokinetics are linear over the recommended daily dose range. Gender does not have a clinically significant influence on the plasma concentrations of pregabalin.

Specialpopulation

Renalimpairment

Pregabalin clearance is directly proportional to creatinine clearance. In addition, pregabalin is effectively removed from plasma by hemodialysis (following 4 hours hemodialysis 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 hemodialysis is necessary.

Hepaticimpairment

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.

Pediatricpopulation

After oral administration of pregabalin in pediatric patients in the fasted state, peak plasma concentration is achieved within 0.5-2 hours. Pregabalin terminal half-life averaged about 3-4 hours in pediatric patients up to 6 years of age and 4-6 hours in those 7 years of age and older.
Creatinine clearance is a significant covariate of pregabalin oral clearance, body weight is a significant covariate of pregabalin apparent oral volume of distribution, and these relationships are similar in pediatric and adult patients. Pregabalin pharmacokinetics in patients younger than 3 months old have not been studied.

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 agerelated compromised renal function.

Breast-feeding

Lactation has 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 doses are approximately 7% of the total daily maternal dose on a mg/kg basis.

5.3 Preclinical safety data *Notapplicable*

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Spray dried lactose
DCL 11
Corn starch
Talc
Capsule shell Leptica 150 mg size 2 (body and cap white op. (44.700))

6.2. Incompatibilities

Notapplicable

6.3. Shelf life

24 months.

Shelf-lifeafterdilution

Notapplicable

6.4 Special precautions for storage
Store at temperature below 30°C.

6.5 Nature and contents of container
Bilster of PVC Film and Aluminium Foil Containing 10 hard capsules Box of 3 blisters

6.6 Special precautions for disposal and other handling
No special requirements for disposal

7. MARKETING AUTHORISATION HOLDER
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8. MARKETING AUTHORISATION NUMBER(S)
TAN 21 HM 0485

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
26/11/2021

10. DATE OF REVISION OF THE TEXT