Summary of Products Characteristics

1. Name of medicinal product

NEUROLIN 300 (Pregabalin Hard Gelatin Capsules 300 mg)

2. Qualitative and quantitative compositions

Each hard gelatin capsule contains:
Pregabalin USP .....300 mg
Excipient with known effect: Lactose
For full list of excipients, see section 6.1

3. Pharmaceutical form

A white color circular shape biconvexed uncoated tablet, plain on both sides.

4. Clinical particulars

4.1. Therapeutics indications

Pregabalin is indicated for the management of pain in painful diabetic peripheral neuropathy and post therapeutic neuralgia. It is also indicated as adjunctive therapy for adult epilepsy patients with partial onset seizures.

4.2. Posology and method of administration

Pregabalin is given orally with or without food.

Adult patients
The recommended pregabalin dosage range for the treatment of neuropathic pain, which includes that associated with DPN and PHN, is 150-600 mg/day administered in two or three divided doses in patients with a creatinine clearance rate of at least 60 mL/min. An initial dosage of 150 mg/day may be increased to 300 mg/ after 3 - 7 days, based on individual patient response and tolerability; if necessary, the dosage can be increased to 600 mg/day (in 2 – 3 divided doses) after an additional 7 days. Pregabalin dosage adjustment should be considered in cases of renal impairment.

As an adjunct for the therapy of partial-onset seizures pregabalin should be started in a daily dose of 150 mg given in 2 or 3 equally divided portions in patients with a creatinine clearance rate of at least 60 mL/min. Based on individual patient response and tolerability, the dose may be increased to a maximum of 600 mg/day. Pregabalin dosage adjustment should be considered in cases of renal impairment.

When discontinuing pregabalin, taper gradually over a minimum of 1 week.

In case of renal impairment in adults, pregabalin dosage adjustment should be considered as per the table below:

Table: Pregabalin Dosage Adjustment Based on Renal Function

Creatinine Clearance (mL/min)	**Total Pregabalin Daily Dose (mg/day)**			**Dose Regimen**
≥ 60	150	300	600	BID or TID
30 – 60	75	150	300	BID or TID
15 – 30	25 – 50	75	150	OD or BID
< 15	25	25 – 50	75	OD
Supplementary dose following hemodialysis[b]				
Patients on the 25 mg OD regimen: Take one supplemental dose of 25 mg or 50 mg				
Patients on the 25 – 50 mg OD regimen: Take one supplemental dose of 50 mg or 75 mg				
Patients on the 75 mg OD regimen: Take one supplemental dose of 100 mg or 150 mg				

TID = three times daily; BID = two times daily; OD = once daily
[a] - Total daily dose should be divided as indicated by the dose regimen
[b] - Supplementary dose is a single additional dose

Elderly patients (>65 years of age):
Pregabalin oral clearance tends to decrease with increasing age. Reduction of pregabalin dose may be required in patients who have age-related compromised renal function. Dose adjustment should be done according to the above table in case of significant renal impairment.

Pediatric patients (<18 years of age):
Pregabalin is not recommended for use in this age group of patients because its safety and efficacy have not yet been evaluated in them.

4.3. Contra-indications

Pregabalin is contraindicated in patients with known hypersensitivity to this drug or any of its components.

4.4. Special warning and precautions for use: WARNINGS

Do not take this product if you are allergic to any ingredient in this product. If you have any medical commodities, pregnancy, or breast-feeding than immediately inform your doctor and further queries regarding the medicine than contact your doctor.

PRECAUTIONS

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

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

Pregabalin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in the elderly population. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medication.

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

In controlled studies, a higher proportion of patients treated with pregabalin reported blurred vision. Although the clinical significance of the ophthalmologic findings is unknown, patients should be informed that if changes in vision occur, they should notify their physician.

Peripheral Edema: As the thiazolidinedione class of antidiabetic drugs can cause weight gain and/or fluid retention, possibly exacerbating or leading to heart failure, care should be taken when co-administering pregabalin and these agents.

Creatine Kinase Elevations: Prescribers should instruct patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if these muscle symptoms are accompanied by malaise or fever. Pregabalin treatment should be discontinued if myopathy is diagnosed or suspected or if markedly elevated creatine kinase levels occur.

4.5. Interaction with other drugs and other forms of interactions

Since pregabalin is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (<2% of a dose recovered in urine as metabolites), does not inhibit drug metabolism in vitro, and is not bound to plasma proteins, 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 pregnancy and lactation

Women of childbearing potential/Contraception in males and females

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

Pregnancy

Studies in animals have shown reproductive toxicity (see section 5.3). Pregabalin has been shown to cross the placenta in rats (see section 5.2). 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 5.2). 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.

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 5.3).

4.7. Effects on ability to drive and operate machine

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	Frequency	Adverse Drug Reactions
Infections and infestations	Common	Nasopharyngitis
Blood and lymphatic disorders	Uncommon	Neutropaenia
Immune system disorders	Uncommon	Hypersensitivity
Immune system disorders	Rare	Angioedema, allergic reaction
Metabolism and nutrition disorders	Common	Appetite increased
Metabolism and nutrition disorders	Uncommon	Anorexia, hypoglycaemia
Psychiatric disorders	Common	Euphoric mood, confusion, irritability, libido decreased, disorientation, insomnia
Psychiatric disorders	Uncommon	Hallucination, panic attack, agitation, depression, aggression, mood swings, abnormal dreams

Psychiatric disorders	Rare	Disinhibition, suicidal behaviour, suicidal ideation
Psychiatric disorders	Not known	Drug dependence
Nervous system disorders	Very common	Dizziness, somnolence, headache
Nervous system disorders	Common	Ataxia, tremor, amnesia, sedation, balance disorder
Nervous system disorders	Uncommon	Syncope, stupor, myoclonus, loss of consciousness, cognitive disorder, malaise
Nervous system disorders	Rare	Convulsions, Parkinsonism
Eye disorders	Common	Vision blurred, diplopia

Eye disorders	Uncommon	Visual disturbance, eye pain, dry eye
Eye disorders	Rare	Vision loss, keratitis
Ear and labyrinth disorders	Common	Vertigo
Ear and labyrinth disorders	Uncommon	Hyperacusis
Cardiac disorders	Uncommon	Tachycardia, bradycardia, congestive heart failure
Cardiac disorders	Rare	QT prolongation, sinus arrhythmia
Vascular disorders	Uncommon	Flushing, hypotension, hypertension
Respiratory disorders	Uncommon	Dyspnoea, cough, nasal congestion
Respiratory disorders	Rare	Pulmonary oedema
Respiratory disorders	Not known	Respiratory depression

Gastrointestinal disorders	Common	Vomiting, nausea, diarrhoea, constipation
Gastrointestinal disorders	Uncommon	GERD, salivary hypersecretion
Gastrointestinal disorders	Rare	Pancreatitis, swollen tongue
Hepatobiliary disorders	Uncommon	Elevated liver enzymes
Hepatobiliary disorders	Rare	Jaundice
Hepatobiliary disorders	Very rare	Hepatic failure, hepatitis
Skin disorders	Uncommon	Rash, urticaria, pruritus
Skin disorders	Rare	Stevens-Johnson syndrome, toxic epidermal necrolysis
Musculoskeletal disorders	Common	Muscle cramp, arthralgia, back pain
Musculoskeletal disorders	Uncommon	Joint swelling, myalgia
Musculoskeletal disorders	Rare	Rhabdomyolysis
Renal and urinary disorders	Uncommon	Urinary incontinence, dysuria
Renal and urinary disorders	Rare	Renal failure, urinary retention
Reproductive disorders	Common	Erectile dysfunction
Reproductive disorders	Uncommon	Ejaculation delayed, sexual dysfunction
Reproductive disorders	Rare	Gynaecomastia, amenorrhoea
General disorders	Common	Fatigue, oedema, gait abnormal
General disorders	Uncommon	Face oedema, pyrexia, chest tightness
Investigations	Common	Weight increased

Investigations	Uncommon	Blood glucose increased, platelet count decreased
Investigations	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. The following symptoms have been reported: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, convulsions, nervousness, depression, suicidal ideation, pain, hyperhidrosis and dizziness. These symptoms may indicate drug 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 (see sections 4.2 and 4.4).

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, 5.1 and 5.2).

Reporting of suspected adverse reactions
Healthcare professional are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Reporting System (PvERS) https://pv.pharmacyboardkenya.org.

4.9. Overdose

In the post-marketing 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).
Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

5. Pharmacological properties

5.1. Pharmaco-dynamic properties

Pregabalin has a similar pharmacological profile to that of gabapentin. It demonstrated antiallodynic and antihyperalgesic activities in various rodent models of neuropathic pain, including: vincristine-, streptozocin-, and nerve injury-induced mechanical allodynia; formalin-, carrageenan-, substance P-, NMDA and thermal injury-induced hyperalgesia; and surgically-induced mechanical allodynia. The exact mechanism of action of pregabalin is unclear. It is a structural analogue of GABA, like gabapentin, although neither compound interacts with GABA-A or -B receptors, or influences GABA uptake.

Pregabalin (and gabapentin) may, however, modulate the presynaptic release of excitatory neurotransmitters, such as glutamate and noradrenaline (norepinephrine), by selectively binding with high affinity to α_2-δ protein, an auxiliary subunit of voltage-gated calcium channels. Both pregabalin and gabapentin modulated the release of the sensory neuropeptides substance P and calcitonin gene-related peptide from rat spinal tissues, but only under conditions that correspond to significant inflammationinduced sensitization of the spinal cord.

5.2. Pharmaco-kinetic properties

Pregabalin steady-state pharmacokinetics is 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.

Metabolism: Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabelled pregabalin, approximately 98% of the radioactivity recovered in the urine was unchanged pregabalin. The N-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0.9% of the dose. In preclinical studies, there was no indication of 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. Dosage adjustment in patients with reduced renal function or undergoing haemodialysis is necessary.

Pharmacokinetics in special patient groups
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, dosage reduction in patients with renal impairment and dosage 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 (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.
Pregnancy and lactation: There are no adequate data on the use of pregabalin in pregnant women.

Studies in animals have shown reproductive toxicity. The potential risk to humans is unknown. Therefore, pregabalin should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus.
It is not known if pregabalin is excreted in the breast milk of humans; however, it is present in the milk of rats. Therefore, breast-feeding is not recommended during treatment with pregabalin.

5.3. Pre-clinical safety data

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.

6. Pharmaceutical particulars

6.1. List of excipients

Hypromellose K15M

Hypromellose K4M

Lactose

Hydroxypropylcellulose

Magnesium stearate

Colloidal Anhydrous silica

6.2. Incompatibilities

Not applicable

6.3. Shelf-life

24 Months

6.4. Special precaution for storage

Store below 30°C. Protect from light and moisture.

6.5. Nature and contents of container

Commercial presentation: 4's, 10's, 20's, 30's & 100's
3 x10's (10 tablets are packed in one Alu-Alu blister and 3 Alu-Alu blister is kept in one carton along with package insert.

7. Marketing authorization holder

M/s. Innocia Lifesciences Pvt. Ltd.

Block D, No. 34/9, Balaji Nagar, Ambattur, Chennai, Tiruvallur
Tamil Nadu, Chennai
600053 India

8. Marketing authorisation number(s)

H2021/CTD6307/1881ER

9. Date of first authorization

20/09/2021

10. Date and revision of text

13/ February/2024