SUMMARY OF PRODUCT CHARACTERISTICS

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SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

[Should the product to which a completed summary of product characteristics (SmPC) be prequalified, it will form Part 4 of the FDA Public Assessment Report that will be posted on the website of FDA.

<text> signifies text to be selected or deleted as appropriate.

{text} refers to information to be added.]

1. Name of the Medicinal Product:

Product Name: LIGABA 150 [PREGABALIN CAPSULES 150 mg]

2. Qualitative and quantitative composition

2.1 Qualitative Declaration:

INGREDIENTS	SPECIFICATION
Pregabalin	IHS
Lactose anhydrous	USPNF
Pregelatinised starch	USPNF
Talc	USPNF
Size '0' empty hard gelatin capsule having yellow color body and red color cap	IHS

2.2 Quantitative Declaration:

INGREDIENTS	SPECIFICATION	QTY/CAPSULE (mg)
Pregabalin	IHS	150.00
Lactose anhydrous	USPNF	290.20
Pregelatinised starch	USPNF	48.00
Talc	USPNF	4.80
Size '0' empty hard gelatin capsule having yellow color body and red color cap	IHS	1 No's

3. Pharmaceutical Form

Size 0 capsules with red color cap and yellow color body filled with white granular powder.

4. Clinical Particulars

4.1 Therapeutic Indications

Pregabalin is indicated for:

- Management of neuropathic pain associated with diabetic peripheral neuropathy
- Management of post herpetic neuralgia
- Adjunctive therapy for adult patients with partial onset seizure s
- Management of fibromyalgia.

4.2 Posology and method of administration

General Dosing Information

Pregabalin is given orally with or without food. When discontinuing Pregabalin, taper gradually over a minimum of 1 week.

Neuropathic pain associated with diabetic peripheral neuropathy

The maximum recommended dose of pregabalin is 100 mg three times a day (300 mg/day) in patients with creatinine clearance of at least 60 mL/min. Begin dosing at 50 Mg three times a day (150 mg/day). The dose may be increased to 300 mg/day within 1 week based on efficacy and tolerability, because Pregabalin is eliminated primarily by renal excretion. Adjust the dose in patients with reduced renal function. In view of the dose-dependent adverse reactions, treatment with doses above 300 Mg/day is not recommended.

Postherpetic neuralgia

The recommended dose of pregabalin is 75to 150 mg two times a day, or 50 to 100 mg three times a day (150 to 300 mg/day) in patients with creatinine clearance of at least 60 mL/min, Begin dosing at 75 mg two times a day, or 50 mg three times a day (150 mg/day). The dose may be increased to 300 mg/day within 1 week based on efficacy and tolerability. Because pregabalin is eliminated primarily by renal excretion, adjust the dose in patients with reduced renal function.

Patients who do not experience sufficient pain relief following 2to 4 weeks of treatment with 300 mg/day, and who are able to tolerate pregabalin , may be treated with up to 300 mg two times a day, or 200 mg three times a day (600 mg/day), In view of the dose-dependent adverse reactions and the higher rate of treatment discontinuation due to adverse reactions, reserve dosing above 300 mg/day for those patients who have on-going pain and are tolerating 300 mg daily.

Adjunctive therapy for adult patients with partial on set seizures

Pregabalin at doses of 150 to 600 mg/day has been shown to be effective as adjunctive therapy in the treatment of partial onset seizures in adults. Both the efficacy and adverse event profiles of pregabalin have been shown to be dose-related. Administer the total daily dose in two or three divided doses. In general it is recommended that patients be started on a

total daily dose no greater than l50mg/day (75 mg two times a day, or 50 mg three times a day). Based on individual patient Response and tolerability, the dose may be increased to a maximum dose of 600 Mg/day.

Because pregabalin is eliminated primarily by renal excretion, adjust the dose in patients with reduced renal function.

The effect of dose escalation rate on the tolerability of pregabalin has not been formally studied.

The efficacy of add-on pregabalin in patients taking gabapentin has not been evaluated in controlled trials. Consequently, dosing recommendations for the use of pregabalin with gabapentin cannot be offered.

Management of Fibromyalgia

The recommended dose of pregabalin for fibromyalgia is 300 to 450 mg/day. Begin dosing at 75 mg two times a day (150 mg/day). The dose 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). Although pregabalin was also studied at 600 mg/day, .there is no evidence that this dose confers additional benefit and this dose was less well tolerated. In view of the dose-dependent adverse reactions, treatment with doses above 450 mg/day is not recommended. Because pregabalin is eliminated primarily by renal excretion, adjust the dose in patients with reduced renal function.

Patients with Renal Impairment

In view of dose-dependent adverse reactions and since pregabalin is eliminated primarily by renal excretion, adjust the dose in patients with reduced renal function. Base the dose adjustment in patients with renal impairment on creatinine clearance (CLcr), as indicated in Table 1. To use this dosing table, an estimate of the patient's CLcr in mL/min is needed. CLcr in mL/min may be estimated from serum creatinine (mg/dL) determination using the Cockcroft and Gault equation:

$$\text{CLCr} = \frac{[140-\text{age(years)}] \times \text{Weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \quad (\times 0.85 \text{ for female patients})$$

Next, refer to the Dosage and Administration section to determine the recommended Total daily dose based on indication, for a patient with normal renal function (CLcr > 60 mL/min). Then refer to Table 1 to determine the corresponding renal adjusted dose. (For example: A patient initiating pregabalin) therapy for postherpetic neuralgia with normal renal function

(CLcr > 60 mL/min), receives a total daily dose of 150 mg/day pregabalin. Therefore, a renal impaired patient with a CLcr of 50 mL/min would receive a total daily dose of 75mg/day pregabalin administered in two or three divided doses,). For patients undergoing hemodialysis, adjust the pregabalin daily dose based on renal function. In addition to the daily dose adjustment, administer a supplemental dose immediately following every 4-hour hemodialysis treatment (see Table 1).

Table 1: Pregabalin Dosage Adjustment Based on Renal Function

Creatinine Clearance (Clcr) (mL/min)	Total Pregabalin Daily Oose (mg/day)*				Dose Regimen
>60	150	300	450	600	BID or TID
30-60	75	150	225	300	BID or TID
1530	2550	75	100-150	150	QD or BID
<15	25	25-50	50-75	75	QD

Supplementary dosage following hemodialysis (mg)+

Patients on the 25 mg QD regimen: take one supplemental dose of 25 mg or 50 mg

Patients on the 25-50 mg QD regimen: take one supplemental dose of 50 mg or 75 mg

Patients on the 50- 75 mg QD regimen take one supplemental dose of 75 mg or 100 mg

Patients on the 75 mg QD regimen: take one supplemental dose of 100 mg or 150 mg

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.

4.3 Contraindications

Pregabalin is contraindicated in patients with known hypersensitivity to pregabalin or any of its components. Angioedema and hypersensitivity reactions have occurred in patients receiving pregabalin therapy.

4.4 Special Warnings and Precautions for Use

Angioedema

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 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.

Withdrawal of Antiepileptic Drugs (AEDs)

As with all AEDs, withdraw pregabalin gradually to minimize the potential of increased Seizure frequency in patients with seizure disorders. If pregabalin is discontinued, taper the drug gradually over a minimum of 1 week.

Suicide at 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.

Inform patients, their caregivers, and families that pregabalin and other AEDs increase the risk of suicidal thoughts and behavior and advise them of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Report behaviors of concern immediately to healthcare providers.

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.

Higher frequencies of weight gain and peripheral edema were observed inpatients taking both pregabalin and a thiazolidinedione antidiabetic agent compared to patients taking either drug alone. 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.

Because there are limited data on congestive heart failure patients with New York Heart Association (NYHA) Class III or IV cardiac status, exercise caution when using pregabalin in these patients.

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.

Weight Gain

Pregabalin treatment may cause weight gain.

Abrupt or Rapid Discontinuation

Following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache, and diarrhea. Taper pregabalin gradually over a minimumof1week rather than discontinuing the drug abruptly.

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 premarketing development provides no direct means to assess its potential for inducing tumors in humans.

In clinical studies across various patient populations, comprising 6396 patient-years of exposure in patients> 12 years of age, new or worsening-preexisting tumors were reported in 57 patients. Without knowledge of the background incidence and recurrence in similar populations not treated with pregabalin, it is impossible to know whether the incidence seen in these cohorts is or is not affected by treatment.

Ophthalmological Effects

In controlled studies, 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 vision-related 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. Instruct patients to promptly report unexplained muscle pain, tenderness or weakness, particularly if these muscle symptoms are accompanied by malaise or lever. 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 x 103/µL, compared to 11 x 103/µL in placebo patients. In the overall database of controlled trials, 2% of placebo patients and 3% of pregabalin patients experienced a potentially clinically significant decrease in platelets, defined as 20% below baseline value and < 150 x 103/µL. A single pregabalin treated subject developed severe thrombocytopenia with a platelet count less than 20 x 103/ µL. In randomized controlled trials, pregabalin was not associated with an increase in bleeding-related adverse reactions.

PR Interval Prolongation

Pregabalin treatment was associated with PR interval prolongation. In analyses of clinical trial ECG data, the mean PR interval increase was 3- 6 msec at pregabalin doses > 300 mg/day. This mean change difference was not associated with an increased risk of PR increase > 25% from baseline, an increased percentage of subjects with on-treatment PR > 200 msec, or an increased risk of adverse reactions of second or third degree AV block.

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.

4.5 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), and does not bind to plasma proteins, its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions or protein binding displacement. In vitro and in *vivo* studies showed that pregabalin is unlikely to be involved in significant pharmacokinetic drug interactions. Specifically, there are no pharmacokinetic interactions between pregabalin and the following antiepileptic drugs: carbamazepine, valproic acid, lamotrigine, phenytoin, phenobarbital, and topiramate. Important pharmacokinetic interactions would also not be expected to occur between pregabalin and commonly used antiepileptic drugs.

Pharmacodynamics

Multiple oral doses of pregabalin were co-administered with oxycodone, lorazepam, or ethanol. Although no pharmacokinetic interactions were seen, additive effects on cognitive and gross motor functioning were seen when pregabalin was co-administered with these drugs. No clinically important effects on respiration were.

4.6 Pregnancy and Lactation

Pregnancy

Pregnancy Category C

Increased incidences of fetal structural abnormalities and other manifestations of developmental toxicity, including Lethality, growth retardation, and nervous and reproductive system functional impairment, were observed in the offspring of rats and rabbits given pregabalin during pregnancy, at doses that produced plasma pregabalin exposures (AUC) > 5 times human exposure at the maximum recommended dose (MRO) 01600 mg/day

There are no adequate and well-controlled studies in pregnant women. Use pregabalin during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known if pregabalin is excreted in human milk; it is, however, present in the milk of rats, Because many drugs are excreted inhuman milk, and bee au se of the potential for tumorigenicity shown for pregabalin in animal studies, decide whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established.

4.7 Effects on Ability to Drive and Use Machines

No impairment of driving or psychometric performance was observed following clopidogrel administration.

4.8 Undesirable Effects

Clinical studies conducted have reported following adverse *eve*nts:

Adverse Reactions Most Commonly leading to Discontinuation

In the pregabalin treatment group, the adverse reactions most frequently leading to discontinuation were dizziness (4%) and somnolence (3%).

Most Common Adverse Reactions

The most common side effects events seen with pregabalin treatment are dizziness, somnolence, headache, ataxia, asthenia, dry mouth, constipation, edema, blurred vision, weight gain, and "thinking abnormal" (primarily difficulty with concentration/attention).

4.9 Overdose

There is limited experience with overdose of pregabalin. The highest reported accidental overdose of pregabalin during the clinical development program was 8000 mg, and there were no notable clinical consequences.

Treatment or Management of Overdose

There is no specific antidote for overdose with pregabalin. If indicated, elimination of unabsorbed drug may be attempted by emesis or gastric lavage; observe usual precautions to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient.

Contact a Certified Poison Control Center for upto-date information on the management of overdose with pregabalin.

Although hemodialysis has not been performed in the few known cases of overdose, if may be indicated by the patient's clinical state or in patients with significant renal impairment. Standard hemodialysis procedures result in significant clearance of pregabalin (approximately50%in4 hours).

5. Pharmacological properties

5.1 Pharmacodynamic Properties

Mechanism of action:

Pregabalin binds with high affinity to the alpha2-delta site (an auxiliary subunit of voltage-gated calcium channels) in central nervous system tissues. Although the mechanism of action of pregabalin has not been fully elucidated, results with genetically modified mice and with compounds structurally related to pregabalin (such as gabapentin) suggest that binding to the alpha2-delta subunit may be involved in pregabalin's anti-nociceptive and antiseizure effects in animals. In animal models of nerve damage, pregabalin has been shown to reduce calcium-dependent release of pro-nociceptive neurotransmitters in the spinal cord, possibly by disrupting alpha2- delta containing-calcium channel trafficking and/or reducing calcium currents. Evidence from other animal models of nerve damage and persistent pain suggest the anti-nociceptive activities of pregabalin may also be mediated through interactions with descending noradrenergic and serotonergic pathways originating from the brain stem that modulate pain transmission in the spinal cord.

While pregabalin is a structural derivative of the inhibitory neurotransmitter gamma amino butyric acid (GABA), it does not bind directly to $GABA_A$, $GABA_B$, or benzodiazepine receptors, does not augment $GABA_A$ responses in cultured neurons, does not alter rat brain

GABA concentration or have acute effects on GABA uptake or degradation. However, in cultured neurons prolonged application of pregabalin increases the density of GABA transporter protein and increases the rate of functional GABA transport. Pregabalin does not block sodium channels, is not active at opiate receptors, and does not alter cyclooxygenase enzyme activity. It is inactive at serotonin and dopamine receptors and does not inhibit dopamine, serotonin, or noradrenaline reuptake.

5.2 Pharmacokinetic Properties

Pregabalin is well absorbed after oral administration, is eliminated largely by renal excretion, and has an elimination half-life of about 6 hours.

Absorption and Distribution:

Following oral administration of pregabalin capsules under fasting conditions, peak plasma concentrations occur within 1.5 hours. Pregabalin oral bioavailability is ≥ 90% and is independent of dose. Following single-(25 to300 mg) and multiple- dose (75 to 900 mg/day) administration, maximum plasma concentrations (C max) and area under the plasma concentration-time curve (AUC) values increase linear1y. Following repeated administration, steady state is achieved within 24 to 48 hours. Multiple-dose pharmacokinetics can be predicted from single-dose data.

The rate of pregabalin absorption is decreased when given with food, resulting in a decrease in Cmax of approximately 25% to 30% and an increase in Tmax to approximately 3 hours, However, administration of pregabalin with food has no clinically relevant effect on the total absorption of pregabalin. Therefore, pregabalin can be taken with or without food.

Pregabalin does not bind to plasma proteins. The apparent volume of distribution of pregabalin following oral administration is approximately 0.5 L/kg. Pregabalin is a substrate for system L transporter which is responsible for the transport of large amino acids across the blood brain barrier. Although there are no data in humans, pregabalin has been shown to cross the blood brain barrier in mice, rats and monkeys. In addition, pregabalin has been shown to cross the placenta in rat s and is present in the milk of lactating rats.

Metabolism and Elimination

Pregabalin undergoes negligible metabolism in humans. Following a dose of radio labeled pregabalin, approximately 90% of the administered dose was recovered in the urine as unchanged pregabalin. The N-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0.9% of the dose

Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug with a mean elimination half-life of 6.3 hours in subjects with normal renal

function. Mean renal clearance was estimated to be 67.0 to 80.9 mL/min in young healthy subjects. Because pregabalin is not bound to plasma proteins this clearance rate indicates that renal tubular reabsorption is involved. Pregabalin elimination is nearly proportional to creatinine clearance (CLcr).

Pharmacokinetics in special populations

Race

In population pharmacokinetic analyses of the clinical studies in various populations, the pharmacokinetics of pregabalin were not significantly affected by race.

Gender

Population pharmacokinetic analyses of the clinical studies showed that the relationship between daily dose and pregabalin drug exposure is similar between genders.

Renal impairment and Hemodialysis

Pregabalin clearance is nearly proportional to creatinine clearance (CLcr). Dosage reduction in patients with renal dysfunction is necessary. Pregabalin is effectively removed from plasma by hemodialysis. Following a 4-hour hemodialysis treatment, plasma pregabalin concentrations are reduced by approximately 50%. For patients on hemodialysis, dosing must be modified.

Elderly

Pregabalin oral clearance tended to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with age-related decreases in CLcr. Reduction of pregabalin dose may be required in patients who have age-related compromised renal function.

Pediatric Pharmacokinetics

Pharmacokinetics of pregabalin have not been adequately studied in pediatric patients.

5.3 Preclinical 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 hypo activity, 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, pregabain 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

Lactose anhydrous USPNF, Pregelatinised starch USPNF, Talc USPNF, Size '0' EHG Capsule having yellow color body and red color cap IHS.

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

24 months from date of manufacture.

6.4 Special precautions for Storage

Keep out of reach of children; Protect form light and moisture; Store below 30°C in a dry place.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

Pregabalin Capsules are available as blister pack of 3x 10's.

6.6 Special precautions for disposal <and other handling>

No special requirements.

7. APPLICANT/SUPPLIER

Mega Lifesciences (Australia) Pty. Ltd.
60, National Avenue Se Business Park,
PAKENHAM, VIC 3810, Australia

8. FDA APPLICATION NUMBER

FDB/SD.173-4183

9. DATE OF <REGISTRATION> / <RENEWAL OF REGISTRATION>

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