
1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product

LARYUL 300 (Pregabalin Capsules BP 300 mg)

2. Qualitative and quantitative composition

Each Hard Gelatin capsule contains:

Pregabalin BP.....300 mg

Excipients.....Q.S.

Approved colours used in capsule shell.

3. Pharmaceutical form

Hard Gelatin capsule

Hard gelatin capsules of size '1' having Red coloured cap & White coloured body containing white crystalline powder.

4. Clinical particulars

4.1 Therapeutic indications

Neuropathic pain

Laryul 300 is indicated for the treatment of peripheral and central neuropathic pain in adults.

Epilepsy

Laryul 300 is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.

Generalised anxiety disorder

Laryul 300 is indicated for the treatment of generalised anxiety disorder (GAD) in adults.

4.2 Posology and method of administration

Posology

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-day 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.

Generalised anxiety disorder

The dose range is 150 to 600 mg per day given as two or three divided doses. The need for treatment should be reassessed regularly. Pregabalin treatment can be started with a dose of 150 mg per day. Based on individual patient response and tolerability, the 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 (see sections Special warnings and precautions for use and Overdose).

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 (see section Pharmacokinetic properties), dose reduction in patients with compromised renal function must be individualised according to creatinine clearance (CL_{cr}), as indicated in Table 1 determined using the following formula:

$$\text{CL}_{\text{cr}} \text{ (ml/min)} = \frac{1.23 \times [140 - \text{age (years)}] \times \text{weight (kg)}}{\text{serum creatinine } (\mu\text{mol/l)}} \quad (\times 0.85 \text{ for female patients})$$

Pregabalin is removed effectively from plasma by haemodialysis (50% of drug in 4 hours). For patients receiving haemodialysis, the pregabalin daily dose should be adjusted based on renal function. In addition to the daily dose, a supplementary dose should be given immediately following every 4 hour haemodialysis treatment (see Table 1).

Table 1. Pregabalin dose adjustment based on renal function

Creatinine clearance (CL _{cr}) (ml/min)	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 haemodialysis (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.

Hepatic impairment

No dose adjustment is required for patients with hepatic impairment (see section Pharmacokinetic properties).

Paediatric 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. Currently available data are described in sections Overdose, Pharmacodynamic properties and Pharmacokinetic properties but no recommendation on a posology can be made.

Elderly

Elderly patients may require a dose reduction of pregabalin due to a decreased renal function (see section Pharmacokinetic properties).

Method of Administration

Laryul 300 may be taken with or without food.

For oral use only.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section List of excipients.

4.4 Special warnings and precautions for use

Diabetic patients

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

Hypersensitivity reactions

There have been reports in the post-marketing experience 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, loss of consciousness, confusion, and mental impairment

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 post-marketing 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 medicinal product.

Vision-related effects

In controlled trials, a higher proportion of patients treated with pregabalin reported blurred vision than did patients treated with placebo which resolved in a majority of cases with continued dosing. In the clinical studies where ophthalmologic testing was conducted, the incidence of visual acuity reduction and visual field changes was greater in pregabalin-treated patients than in placebo-treated patients; the incidence of fundoscopic changes was greater in placebo-treated patients (see section Pharmacodynamic properties).

In the post-marketing experience, visual adverse reactions have also 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.

Renal failure

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

Withdrawal of concomitant anti-epileptic medicinal products

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

Withdrawal symptoms

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, diarrhoea, flu syndrome, nervousness, depression, pain, convulsion, hyperhidrosis and dizziness, suggestive of physical dependence. The patient should be informed about this at the start of the treatment.

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

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

Congestive heart failure

There have been post-marketing 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.

Treatment of central neuropathic pain due to spinal cord injury

In the treatment of central neuropathic pain due to spinal cord injury the incidence of adverse reactions in general, central nervous system adverse reactions and especially somnolence was increased. This may be attributed to an additive effect due to concomitant medicinal products (e.g. anti-spasticity agents) needed for this condition. This should be considered when prescribing pregabalin in this condition.

Respiratory depression

There have been reports of severe respiratory depression in relation to pregabalin use. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment, concomitant use of CNS depressants and the elderly may be at higher risk of experiencing this severe adverse reaction. Dose adjustments may be necessary in these patients (see section Posology and method of administration).

Suicidal ideation and behaviour

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled studies of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. 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 behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Reduced lower gastrointestinal tract function

There are post-marketing reports of events related to reduced lower gastrointestinal tract function (e.g. intestinal obstruction, paralytic ileus, constipation) when pregabalin was co-administered 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).

Concomitant use with opioids

Caution is advised when prescribing pregabalin concomitantly with opioids due to risk of CNS depression (see section Interaction with other medicinal products and other forms of interaction). In a case-control study of opioid users, those patients who took pregabalin concomitantly with an opioid had an increased risk for opioid-related death compared to opioid use alone (adjusted odds ratio [aOR], 1.68 [95% CI, 1.19 – 2.36]). This increased risk was observed at low doses of pregabalin (≤ 300 mg, aOR 1.52 [95% CI, 1.04 – 2.22]) and

there was a trend for a greater risk at high doses of pregabalin (> 300 mg, aOR 2.51 [95% CI 1.24 – 5.06]).

Misuse, abuse potential or dependence

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

Encephalopathy

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

Lactose intolerance

Laryul 300 contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total 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 *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 post-marketing 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 Fertility, pregnancy and lactation

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 Preclinical safety data).

Pregnancy

There are no adequate data from the use of pregabalin in pregnant women. Studies in animals have shown reproductive toxicity (see section Preclinical safety data). 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 foetus).

Breast-feeding

Pregabalin is excreted into human milk (see section Pharmacokinetic properties). 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.

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 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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 Special warnings and precautions for use).

Additional reactions reported from post-marketing experience are included in *italics* in the list below.

Table 2. Pregabalin Adverse Drug Reactions

System Organ Class	Adverse drug reactions
Infections and infestations	
Common	Nasopharyngitis
Blood and lymphatic system disorders	
Uncommon	Neutropaenia
Immune system disorders	
Uncommon	<i>Hypersensitivity</i>
Rare	<i>Angioedema, allergic reaction</i>
Metabolism and nutrition disorders	
Common	Appetite increased
Uncommon	Anorexia, hypoglycaemia
Psychiatric disorders	
Common	Euphoric mood, confusion, irritability, disorientation, insomnia, libido decreased
Uncommon	Hallucination, panic attack, restlessness, agitation, depression, depressed mood, elevated mood, <i>aggression</i> , mood swings, depersonalisation, 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, hypoaesthesia, sedation, balance disorder, lethargy
Uncommon	Syncope, stupor, myoclonus, <i>loss of consciousness</i> , psychomotor hyperactivity, dyskinesia, dizziness postural, intention tremor, nystagmus, cognitive disorder, <i>mental impairment</i> , speech disorder, hyporeflexia, hyperaesthesia, burning sensation, ageusia, <i>malaise</i>
Rare	<i>Convulsions</i> , parosmia, hypokinesia, dysgraphia, parkinsonism
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	<i>Vision loss</i> , <i>keratitis</i> , 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, <i>congestive heart failure</i>
Rare	<i>QT prolongation</i> , sinus tachycardia, sinus arrhythmia
Vascular disorders	
Uncommon	Hypotension, hypertension, hot flushes, flushing, peripheral coldness
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness
Rare	<i>Pulmonary oedema</i> , throat tightness
Not known	Respiratory depression
Gastrointestinal disorders	
Common	Vomiting, <i>nausea</i> , constipation, <i>diarrhoea</i> , flatulence, abdominal distension, dry mouth
Uncommon	Gastrooesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral
Rare	Ascites, pancreatitis, <i>swollen tongue</i> , dysphagia
Hepatobiliary disorders	
Uncommon	Elevated liver enzymes*
Rare	Jaundice
Very rare	Hepatic failure, hepatitis
Skin and subcutaneous tissue disorders	

Uncommon	Rash papular, urticaria, hyperhidrosis, <i>pruritus</i>
Rare	<i>Stevens-Johnson syndrome</i> , 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, <i>urinary retention</i>
Reproductive system and breast disorders	
Common	Erectile dysfunction
Uncommon	Sexual dysfunction, ejaculation delayed, dysmenorrhoea, breast pain
Rare	Amenorrhoea, breast discharge, breast enlargement, <i>gynaecomastia</i>
General disorders and administration site conditions	
Common	Oedema peripheral, oedema, gait abnormal, fall, feeling drunk, feeling abnormal, fatigue
Uncommon	Generalised oedema, <i>face oedema</i> , 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

* 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 in some patients. The following reactions have been mentioned: insomnia, headache, nausea, anxiety, diarrhoea, 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, data suggest that the incidence and severity of withdrawal symptoms may be dose-related.

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 Posology and method of administration, Pharmacodynamic properties and Pharmacokinetic properties).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

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 Posology and method of administration Table 1).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-epileptics, other anti-epileptics

ATC code: N03AX16

Mechanism of Action

Pregabalin binds to the $\alpha 2$ - δ subunit of the voltage-gated calcium channels in central nervous system tissues. *In vitro*, pregabalin reduces calcium influx at nerve terminals, which may inhibit the release of excitatory neurotransmitters such as glutamate. Through this mechanism, pregabalin may modulate nerve impulses involved in the transmission of pain. However, the clinical relevance of these findings in man is unknown.

Pharmacodynamics

Pregabalin binds with high affinity to the alpha2-delta protein (a calcium channel subunit) of brain tissues and has analgesic, antiepileptic, and anxiolytic activity. Pregabalin is known chemically as (S)-3-(amino methyl)-5-methylhexanoic acid.

Although the mechanism of action of pregabalin is unknown, results with genetically

modified mice and with compounds structurally-related to pregabalin indicate that selective binding to the alpha2-delta protein is required for analgesic, antiepileptic and anxiolytic action in animal models. *In vitro*, pregabalin reduces the release of several neurotransmitters, suggesting a modulatory action on calcium channel function.

Pregabalin does not mimic GABA at GABAA or GABAB receptors, nor does it augment GABAA responses like benzodiazepines or barbiturates. In contrast to vascular calcium channel blockers, pregabalin does not alter systemic blood pressure or cardiac function. Various *in vitro* and *in vivo* results differentiate pregabalin from GABA uptake inhibitors or GABA transaminase inhibitors. In addition, pregabalin does not block sodium channels, it is not active at opiate receptors, it does not alter cyclooxygenase enzyme activity, it is not a serotonin agonist, it is not a dopamine antagonist, and it is not an inhibitor of dopamine, serotonin or noradrenaline reuptake.

Pregabalin treatment reduces pain-related behavior in neuropathic animal models of diabetes, peripheral nerve damage or chemotherapeutic insult and in a model of musculoskeletal-associated pain. Pregabalin given intrathecally prevents pain-related behaviors and reduces pain-related behavior caused by spinally administered agents, suggesting that it acts directly on tissues of the spinal cord or brain.

5.2 Pharmacokinetic properties

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

Absorption

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

Distribution

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

Biotransformation

Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabelled pregabalin, approximately 98% of the radioactivity recovered in the urine was unchanged pregabalin.

The N- methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0.9% of the dose. In preclinical studies, there was no indication of racemisation of pregabalin S-enantiomer to the R-enantiomer.

Elimination

Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. Pregabalin mean elimination half-life is 6.3 hours. Pregabalin plasma clearance and renal clearance are directly proportional to creatinine clearance (see section Pharmacokinetic properties Renal impairment). Dose adjustment in patients with reduced renal function or undergoing haemodialysis is necessary (see section Posology and method of administration Table 1).

Linearity/non-linearity

Pregabalin pharmacokinetics are linear over the recommended daily dose range. Inter-subject 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.

Gender

Clinical trials indicate that gender does not have a clinically significant influence on the plasma concentrations of pregabalin.

Renal impairment

Pregabalin clearance is directly proportional to creatinine clearance. In addition, pregabalin is effectively removed from plasma by haemodialysis (following a 4 hour haemodialysis treatment plasma pregabalin concentrations are reduced by approximately 50%). Because renal elimination is the major elimination pathway, dose reduction in patients with renal impairment and dose supplementation following haemodialysis is necessary (see section Posology and method of administration Table 1).

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.

Paediatric population

Pregabalin pharmacokinetics were evaluated in paediatric patients with epilepsy (age groups: 1 to 23 months, 2 to 6 years, 7 to 11 years and 12 to 16 years) at dose levels of 2.5, 5, 10 and 15 mg/kg/day in a pharmacokinetic and tolerability study.

After oral administration of pregabalin in paediatric patients in the fasted state, in general, time to reach peak plasma concentration was similar across the entire age group and occurred 0.5 hours to 2 hours postdose.

Pregabalin C_{max} and AUC parameters increased in a linear manner with increasing dose within each age group. The AUC was lower by 30% in paediatric patients below a weight of 30 kg due to an increased body weight adjusted clearance of 43% for these patients in comparison to patients weighing ≥ 30 kg.

Pregabalin terminal half-life averaged about 3 to 4 hours in paediatric patients up to 6 years of age, and 4 to 6 hours in those 7 years of age and older.

Population pharmacokinetic analysis showed that creatinine clearance was a significant covariate of pregabalin oral clearance, body weight was a significant covariate of pregabalin apparent oral volume of distribution, and these relationships were similar in paediatric and adult patients.

Pregabalin pharmacokinetics in patients younger than 3 months old have not been studied (see sections Posology and method of administration, Overdose and Pharmacodynamic properties).

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 age related compromised renal function (see section Posology and method of administration Table 1).

Breast-feeding mothers

The pharmacokinetics of 150 mg pregabalin given every 12 hours (300 mg daily dose) was evaluated in 10 lactating women who were at least 12 weeks postpartum. 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 infant dose from breast milk (assuming mean milk consumption of 150 ml/kg/day) of women receiving 300 mg/day or the maximum dose of 600 mg/day would be 0.31 or 0.62 mg/kg/day, respectively. These estimated doses are approximately 7% of the total daily maternal dose on a mg/kg basis.

5.3 Preclinical safety data

Carcinogenesis

A dose-dependent increase in the incidence of malignant vascular tumors (hemangiosarcomas) was observed in 2 strains of mice (B6C3F1 and CD-1) given pregabalin (200, 1000, or 5000 mg/kg) in the diet for 2 years. Plasma pregabalin exposure (AUC) in mice receiving the lowest dose that increased hemangiosarcomas was approximately equal to the human exposure at the maximum recommended human dose (MRD) of 660 mg/day. A no-effect dose for induction of hemangiosarcomas in mice was not established. No evidence of carcinogenicity was seen in 2 studies in Wistar rats following dietary administration of pregabalin for 2 years at doses (50, 150, or 450 mg/kg in males and 100, 300, or 900 mg/kg in females) that were associated with plasma exposures in males and females up to approximately 15 and 26 times, respectively, human exposure at the MRD.

Mutagenesis

Pregabalin was not mutagenic in bacteria or in mammalian cells *in vitro*, was not clastogenic in mammalian systems *in vitro* and *in vivo*, and did not induce unscheduled DNA synthesis in mouse or rat hepatocytes.

Impairment of Fertility

In fertility studies in which male rats were orally administered pregabalin (50 to 2500 mg/kg) prior to and during mating with untreated females, a number of adverse reproductive and developmental effects were observed. These included decreased sperm counts and sperm motility, increased sperm abnormalities, reduced fertility, increased preimplantation embryo loss, decreased litter size, decreased fetal body weights, and an increased incidence of fetal abnormalities. Effects on sperm and fertility parameters were reversible in studies of this duration (3–4 months). The no-effect dose for male reproductive toxicity in these studies (100 mg/kg) was associated with a plasma pregabalin exposure (AUC) approximately 4 times human exposure at the MRD of 660 mg/day.

In addition, adverse reactions on reproductive organ (testes, epididymides) histopathology were observed in male rats exposed to pregabalin (500 to 1250 mg/kg) in general toxicology studies of 4 weeks or greater duration. The no-effect dose for male reproductive organ histopathology in rats (250 mg/kg) was associated with a plasma exposure approximately 10 times human exposure at the MRD.

In a fertility study in which female rats were given pregabalin (500, 1250, or 2500 mg/kg) orally prior to and during mating and early gestation, disrupted estrous cyclicity and an increased number of days to mating were seen at all doses, and embryo lethality occurred at

the highest dose. The low dose in this study produced a plasma exposure approximately 10 times that in humans receiving the MRD. A no-effect dose for female reproductive toxicity in rats was not established.

6. Pharmaceutical particulars

6.1 List of excipients

Lactose, Maize Starch, Colloidal Silicon Dioxide, Sodium Lauryl Sulphate, Purified Talc & EHG '1' Red/White.

6.2 Incompatibilities

None known.

6.3 Shelf life

Three years from the date of manufacture.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.6 Nature and contents of container

LARYUL 300 is a Hard gelatin capsules of size '1' having Red coloured cap & White coloured body containing white crystalline powder. They are available in printed aluminium foil and plain aluminium foil blister containing 10 capsules.

7. Marketing authorisation holder

GENEITH PHARM LTD.

12 Adewale Crescent, Off Ewenla Street,
Off, Oshodi, Apapa, Lagos,
Nigeria.

8. Marketing authorisation number(s)

BD/26 18/04/2023

9. Date of first authorisation/renewal of the authorisation

18/04/2023

10. Date of revision of the text

17/03/2028