

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

PREGABANEURINE 75 mg hard capsules

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 75 mg of pregabalin

### Excipient(s) with known effect

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Hard capsule

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

#### Neuropathic pain

PREGABANEURINE is indicated for the treatment of peripheral and central neuropathic pains in adults.

#### Epilepsy

PREGABANEURINE is indicative as adjunctive therapy in adults with partial seizures with or without secondary generalisation.

#### Generalised anxiety disorder

PREGABANEURINE 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.

#### *General 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 section 4.4 and 4.8).

### 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 5.2), dose reduction in patients with compromised renal function must be individualised according to creatinine clearance (CL<sub>cr</sub>) as indicated in Table 1 determined using the following formula:

$$Cl_{cr} (ml/min) = \left[ \frac{1.23 \times [140 - \text{age (years)}] \times \text{weight (kg)}}{\text{Serum creatinine } (\mu\text{mol/l})} \right] \times (0.85 \text{ for female patients})$$

Pregabalin is removed effectively from plasma by haemodialysis (50 % 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 <sub>cr</sub> ) (ml/min)	Total pregabalin daily dose*		Dose regimen
	Starting dose (mg/jour)	Maximum dose (mg/jour)	
≥ 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 <sup>†</sup>

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

<sup>†</sup>Supplementary dose is a single additional use

### Hepatic impairment

No dose adjustment is required for patients with hepatic impairment (see section 5.2).

### Paediatric population

The safety and efficacy of PREGABANEURINE in children below the age of 2 years and in adolescents (12-17 years of age) have not been established. Currently available data are described in section 4.8, 5.1 and 5.2 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 5.2).

### Method of administration

PREGABANEURINE may be taken with or without food.

PREGABANEURINE is for oral use only.

## **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

#### **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 postmarketing experience of hypersensitivity reactions, including cases of angioedema. Pregabalin should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper airways swelling occur.

##### Serious skin adverse reactions

Rare cases of serious cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which may be life-threatening or fatal, have been reported in the setting of pregabalin therapy. At the time of prescription, patients should be informed of the signs and symptoms and should be closely monitored for skin reactions.

If signs and symptoms suggestive of these reactions occur, pregabalin should be discontinued immediately and replacement therapy considered (if appropriate).

##### 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 elderly population. There have been postmarketing 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 when ophthalmologic testing was conducted, the incidence of visual acuity reduction and visual field changes was greater in pregabalin-treated than in placebo-treated patients; the incidence of fundoscopic changes was greater in placebo-treated patients (see section 5.1).

In the postmarketing 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 product, 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 patients should be informed about this at the start of the treatment.

Convulsions, including astatus 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 postmarketing 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 neuroapthic 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 conditions. This should be considered when prescribing pregabalin in this condition.

#### Respiratory depression

Cases of severe respiratory depression have been reported in association with the use of pregabalin. Patients with impaired respiratory function or suffering from a respiratory condition or neurological disease, renal insufficiency, or using in combination central nervous system depressant drugs as well as the elderly may be at greater risk of developing this serious side effect. Dose adjustment may be necessary for these patients (see section 4.2).

#### 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 of 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 postmarketing 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 4.5). 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 ( $\leq 300$  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 and 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.

#### Women of childbearing potential/Contraception

pregabaneurine use in the first trimester of pregnancy may cause major birth defects in the unborn child. Pregabalin should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus. Women of childbearing potential have to use effective contraception during treatment (see section 4.6).

#### Lactose intolerance

PREGABALINE contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose=galactose malabsorption should not take this medicinal product.

### **4.5 Interaction with other medicinal products and other forms of interaction**

Since pregabalin est 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 vitro studies and population pharmacokinetic analysis

Accordingly, in *in vitro* 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 meical products

Pregabalin may potentiate the effects of ethanol and lorazepam. In controlled clinical trials, multiple oral doses of pregabalin co-administered with oxycodone, lorazepam, or ethanol did not result in clinically important effects on respiration. In the postmarketing experience, there are reports of respiratory failure and coma in patients taking pregabalin and 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.

#### Interaction 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**

#### Woman with childbearing potential/Contraception

As the potential risk for humans is unknown, effective contraception must used in woman of child bearing potential.

#### Pregnancy

There are no adequate data from the use of prgabalin in pregnant woman.

Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

PREGABANEURINE should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the foetus).

#### 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.

Pregabaneurine 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 use machines**

PREGABANEURINE may have minor or moderate influence on the ability to drive and use machines. PREGABANEURINE may cause dizziness and somnolence and therefore may influence the ability to drive or use machines. Patients are advised not to drive, operate 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-blinded 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 4.4).

Additional reactions reported from postmarketing experience are included in italics in the list below.

**Table 2. Pregabalin Adverse Drug Reactions**

<b>System Organ Class</b>	<b>Adverse drug reaction</b>
<b>Infections and infestations</b>	
Common	Nasopharyngitis
<b>Blood and lymphatic system disorders</b>	
Uncommon	Neutropenia
<b>Immune system disorders</b>	
Uncommon	<i>Hypersensitivity</i>
Rare	<i>Angioedema, allergic reaction</i>
<b>Metabolism and nutrition disorders</b>	
Common	Appetite increased
Uncommon	Anorexia, hypoglycaemia
<b>Psychiatric disorders</b>	
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 suicidal behaviour, suicidal ideation
Not known	<i>Drug dependence</i>
<b>Nervous system disorders</b>	
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, <i>loss of consciousness</i> , psychomotor hyperactivity, dyskinesia, dizziness postural, intention tremor, nystagmus, cognitive disorder, <i>mental impairment</i> , speech disorder, hyporeflexia, burning sensation, agueusia, <i>malaise</i>
Rare	<i>Convulsions</i> , parosmia, hypokinesia, dysgraphia
<b>Eye disorders</b>	
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, keratitis</i> , oscillopsia, altered visual depth perception, mydriasis, strabismus, visual brightness
<b>Ear and labyrinth disorders</b>	
Common	Vertigo



Uncommon	Hyperacusis
<b>Cardiac disorders</b>	
Uncommon	Tachycardia, atrioventricular block first degree, sinus bradycardia, <i>congestive heart failure</i>
Rare	<i>QT prolongation</i> , sinus tachycardia, sinus arrhythmia
<b>Vascular disorders</b>	
Uncommon	Hypotension, hypertension, hot flushes, flushing, peripheral coldness
<b>Respiratory, thoracic and mediastinal disorders</b>	
Uncommon	Dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness
Rare	<i>Pulmonary oedema</i> , throat tightness
<b>Gastrointestinal disorders</b>	
Common	Vomiting, <i>nausea</i> , constipation, <i>diarrhoea</i> , flatulence, abdominal distension, dry mouth
Uncommon	Gastroesophageal reflux disease, salivary hypersecretion, hypoesthesia oral
Rare	Ascites, pancreatitis, <i>swollen tongue</i> , dysphagia
<b>Hepatobiliary disorders</b>	
Uncommon	Elevated liver enzymes*
Rare	Jaundice
Very rare	Hepatic failure, hepatitis
<b>Skin and subcutaneous tissue disorders</b>	
Uncommon	Rash papular, urticaria, hyperhidrosis, <i>pruritus</i>
Rare	<i>Toxic epidermal necrolysis Stevens Johnson syndrome</i> , cold sweat
<b>Musculoskeletal and connective tissue disorders</b>	
Common	Muscle cramp, arthralgia, back pain, pain in limb, cervical spasm
Uncommon	Joint swelling, myalgia, muscle twitching, neck pain, muscle stiffness
Rare	Rhabdomyolysis
<b>Renal and urinary disorders</b>	
Uncommon	Urinary incontinence, dysuria
Rare	Renal failure, oliguria, <i>urinary retention</i>
<b>Reproductive system and breast disorders</b>	
Common	Erectile dysfunction
Uncommon	Sexual dysfunction, ejaculation delayed, dysmenorrhea, breast pain
Rare	Amenorrhea, breast discharge, breast enlargement, <i>gynecomastia</i>
<b>General disorders and administration site conditions</b>	
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
<b>Investigations</b>	
Common	Weight increased
Uncommon	Blood creatinine 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 three paediatric studies in patients with partial seizures with or without secondary generalisation (12-week efficacy and safety study in patients with partial onset seizures, n = 295; pharmacokinetic and tolerability study, n = 65; and 1 year open label follow on safety study n = 54) 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 (see section 4.2, 5.1 and 5.2).

#### 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 via the national reporting system.

### **4.9 Overdose**

In the postmarketing 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 included general supportive measures and may include haemodialysis if necessary (see section 4.2 Table 1).

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Anti-epileptics, other anti-epileptics, ATC code: N03AX16

The active substance, pregabalin, is a gamma-aminobutyric acid analogue [(S)-3-(aminomethyl)-5-methylhexanoic acid].

#### Mechanism of action

Pregabalin binds to an auxiliary subunit ( $\alpha_2\text{-}\delta$  protein) of voltage-gated calcium channels in the central nervous system.

#### Clinical efficacy and safety

##### *Neuropathic pain*

Efficacy has been shown in trials in diabetic neuropathy, post herpetic neuralgia and spinal cord injury. Efficacy has not been studied in other models of neuropathic pain.

Pregabalin has been studied in 10 controlled clinical trials of up to 13 weeks with twice a day dosing (BID) and up to 8 weeks with three times a day (TID) dosing. Overall, the safety and efficacy profiles for BID and TID dosing regimen were similar.

In clinical trials up to 12 weeks for both peripheral and central neuropathic pain, a reduction in pain was seen by Week 1 and was maintained throughout the treatment period.

In controlled clinical trials in peripheral neuropathic pain 35 % of the pregabalin treated patients and 18 % of the patients on placebo had a 50 % improvement in pain score. For patients not experiencing somnolence, such an improvement was observed in 33 % of patients treated with pregabalin and 18 % of patients on placebo. For patients who experienced somnolence the responder rates were 48 % on pregabalin and 16 % on placebo.

In the controlled clinical trial in central neuropathic pain 22 % of the pregabalin treated patients and 7 % of the patients on placebo had a 50 % improvement in pain score.

### *Epilepsy*

#### Adjunctive Treatment

Pregabalin has been studied in 3 controlled clinical trials of 12 week duration with either BID or TID dosing. Overall, the safety and efficacy profiles for BID and TID dosing regimens were similar.

A reduction in seizures frequency was observed by Week 1.

#### Paediatric population

The efficacy and safety of pregabalin as adjunctive treatment for epilepsy in paediatric patients below the age of 12 and adolescent has not been established. The adverse events observed in a pharmacokinetic and tolerability study that enrolled patients from 3 months to 16 years of age (n = 65) with partial onset seizures were similar to those observed in adults. Results of a 12-week placebo-controlled study of 295 paediatric patients aged 4 to 16 years performed to evaluate the efficacy and safety of pregabalin as adjunctive therapy for the treatment of partial onset seizures and a 1 year open label safety study in 54 paediatric patients from 3 months to 16 years of age with epilepsy indicate that the adverse events of pyrexia and upper respiratory infections were observed more frequently than in adults studies of patients with epilepsy (see sections 4.2, 4.8 and 5.2).

In the 12-week placebo-controlled study, paediatric patients were assigned to pregabalin 2.5 mg/kg/day (maximum, 150 mg/day), pregabalin 10 mg/kg/day (maximum, 600 mg/day), or placebo. The percentage of subjects with at least a 50 % reduction in partial onset seizures as compared to baseline was 40.6 % of subjects treated with pregabalin 10 mg/kg/day (p = 0.0068 versus placebo), 29.1 % of subjects treated with pregabalin 2.5 mg/kg/day (p = 0.2600 versus placebo) and 22.6 % of those receiving placebo.

#### Monotherapy (newly diagnosed patients)

Pregabalin has been studied in 1 controlled clinical trial of 56 week duration with BID dosing. Pregabalin did not achieve non-inferiority to lamotrigine based on the 6-month seizure freedom endpoint. Pregabalin and lamotrigine were similarly safe and well tolerated.

#### Generalised Anxiety Disorder

Pregabalin has been studied in 6 controlled trials of 4-6 week duration, an elderly study of 8 week duration and a long term relapse prevention study with a double-blind relapse prevention phase of 6 month duration.

Relief of the symptoms of GAD as reflected by the Hamilton Anxiety Rating Scale (HAM-A) was observed by Week 1.

In controlled clinical trials (4-8 week duration) 52 % of the pregabalin treated patients and 38 % of the patients on placebo had at least a 50 % improvement in HAM-A total score from baseline to endpoint.

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. Ophthalmologic testing (including visual acuity testing, formal visual field testing and dilated

fundoscopic examination) was conducted in over 3,600 patients within controlled clinical trials. In these patients, visual activity was reduced in 6.5 % of patients treated with pregabalin and 4.8 % of placebo-treated patients. Visual field changes were detected in 12.4 % of pregabalin-treated, and 11.7 % of placebo-treated patients. Fundoscopic changes were observed in 1.7 % of pregabalin-treated patients and 2.1 % of placebo-treated patients.

## **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 5.2 Renal impairment).

Dose adjustment in patients with reduced renal function or undergoing haemodialysis is necessary (see section 4.2 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 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 4.2 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 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 parameter 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  $\geq 30$  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 4.2, 4.8 and 5.1).

### 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 4.2 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 concentration approximately 76 % of those in maternal plasma. The estimated infant dose from breast milk (assuming mean milk consumption of 150 ml/kg/day) of a woman receiving 300 mg/day or the maximum dose of 600 mg/day would be 0.31 or 0.62 mg/kg/day, respectively. The estimated doses are approximately 7 % of the total daily maternal dose on a mg/kg basis.

## **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 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  $\geq 5$  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 hemangiosarcoma 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). Effect 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 monohydrate, talc, maize starch, capsules size 2, titanium dioxide (E171).

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years.

### **6.4 Special precautions for storage**

Store in the original container, below 30 °C.

### **6.5 Nature and contents of container**

3 PVC/aluminium blisters containing 10 hard capsules (box of 30 capsules), packaged in a cardboard box.

### **6.6 Special precautions for disposal**

No special requirements for disposal.

## **7. MARKETING AUTHORISATION HOLDER**

Expfar s.a.

Zoning Industriel de Nivelles Sud, zone II – Avenue Thomas Edison 105 – 1402 Thines  
BELGIUM

**8. CATEGORY OF DISTRIBUTION**

Over-the counter medicine                       Prescription only medicines  
List I

**9. MANUFACTURER**

Gracure Pharmaceuticals Ltd.,  
E-1105, Industrial Area, Phase-III, Bhiwadi, Dist. Alwar (Raj.)  
INDIA

**10. DATE OF REVISION OF THE TEXT**

July 2023