

## **SUMMARY OF PRODUCT CHARACTERISTICS(SPC)**

### **1. NAME OF THE MEDICINAL PRODUCT**

SEREMAX-75 SR TABLET

### **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each hard gelatin capsule contains:

Pregabalin.....75 mg

For the full list of excipients, See Section 6.1

### **3. PHARMACEUTICAL FORM**

Capsule for Oral Administration.

### **4. CLINICAL PARTICULARS**

#### **4.1 Therapeutic indications**

Neuropathic pain

SEREMAX-75 SR is indicated for the treatment of peripheral and central neuropathic pain in adults.

Epilepsy

SEREMAX-75 SR is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.

Generalized Anxiety Disorder

SEREMAX-75 SR 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 4.4 and 4.8).

### Patients with renal impairment

Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. As pregabalin clearance is directly proportional to creatinine clearance (see section 5.2), dose reduction in patients with compromised renal function must be individualized according to creatinine clearance (CL<sub>cr</sub>), as indicated in Table 1 determined using the following formula:

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

Pregabalin is removed effectively from plasma by haemodialysis (50% 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

| <b>Creatinine clearance (CL<sub>cr</sub>) mL/min</b> | <b>Starting dose (mg/day)</b> | <b>Maximum dose (mg/day)</b> | <b>Dose regimen</b> |
|------------------------------------------------------|-------------------------------|------------------------------|---------------------|
| <b>≥ 60</b>                                          | 150                           | 600                          | BID or TID          |
| <b>≥ 30 – &lt;60</b>                                 | 75                            | 300                          | BID or TID          |
| <b>≥ 15 – &lt;30</b>                                 | 25–50                         | 150                          | Once daily or BID   |
| <b>&lt;15</b>                                        | 25                            | 75                           | Once daily          |
| <b>Supplementary dose following haemodialysis</b>    | 25                            | 100                          | Single dose*        |

TID = Three divided doses BID = Two divided doses

\* Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose

+ Supplementary dose is a single additional dose

**Patients with hepatic impairment**

No dose adjustment is required for patients with hepatic impairment.

**Paediatric population**

The safety and efficacy of SEREMAX-75 SR in children below the age of 12 years and in adolescents (12-17 years of age) have not been established. No data are available.

Elderly (over 65 years of age) population

Elderly patients may require a dose reduction of pregabalin due to a decreased renal function (see patients with renal impairment). Method of administration SEREMAX-75 SR may be taken with or without food. SEREMAX-75 SR is for oral use only.

**4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipient

**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 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.

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 antiepileptic medicinal products**

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

#### **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. 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.

#### **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).

### **Abuse potential**

Cases of abuse 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 abuse.

### **Encephalopathy**

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

### **Lactose intolerance**

SEREMAX-75 SR 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 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.

### CNS influencing medical 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 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 Pregnancy and lactation**

### Women of childbearing potential / Contraception in males and females

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

### Pregnancy

There are no adequate data from the use of pregabalin in pregnant women. Studies in animals have shown reproductive toxicity.

The potential risk for humans is unknown.

SEREMAX-75 SR 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

It is not known if pregabalin is excreted in the breast milk of humans; however, it is present in the milk of rats. Therefore, breast-feeding is not recommended during treatment with pregabalin.

### 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

## **4.7 Effects on ability to drive and use machines**

SEREMAX-75 SR may have minor or moderate influence on the ability to drive and use machines. SEREMAX-75 SR 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 8900 patients who were exposed to pregabalin, of whom over 5600 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 the table 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 post-marketing experience are included in *italics* in the list below.

| <b>System Organ Class</b>                   | <b>Adverse drug reactions</b>                                                                                                                                                                                                                                        |
|---------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Infections and infestations</b>          |                                                                                                                                                                                                                                                                      |
| Common                                      | Nasopharyngitis                                                                                                                                                                                                                                                      |
| <b>Blood and lymphatic system disorders</b> |                                                                                                                                                                                                                                                                      |
| Uncommon                                    | Neutropaenia                                                                                                                                                                                                                                                         |
| <b>Immune system disorders</b>              |                                                                                                                                                                                                                                                                      |
| Uncommon                                    | Hypersensitivity                                                                                                                                                                                                                                                     |
| Rare                                        | Angioedema, allergic reaction                                                                                                                                                                                                                                        |
| <b>Metabolism and nutrition disorders</b>   |                                                                                                                                                                                                                                                                      |
| Common                                      | Appetite increased                                                                                                                                                                                                                                                   |
| Uncommon                                    | Anorexia, hypoglycaemia                                                                                                                                                                                                                                              |
| <b>Psychiatric disorders</b>                |                                                                                                                                                                                                                                                                      |
| Common                                      | Euphoric mood, confusion, irritability, libido decreased, disorientation, insomnia                                                                                                                                                                                   |
| Uncommon                                    | Hallucination, panic attack, restlessness, agitation, depression, depressed mood, elevated mood, aggression, mood swings, depersonalisation, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy                                          |
| Rare                                        | Disinhibition, suicidal behaviour, suicidal ideation                                                                                                                                                                                                                 |
| Not known                                   | Drug dependence (see section 4.4)                                                                                                                                                                                                                                    |
| <b>Nervous system disorders</b>             |                                                                                                                                                                                                                                                                      |
| 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, loss of consciousness, psychomotor hyperactivity, dyskinesia, dizziness postural, intention tremor, nystagmus, cognitive disorder, mental impairment, speech disorder, hyporeflexia, hyperaesthesia, burning sensation, ageusia, malaise |
| Rare                                        | Convulsions, hypokinesia, parosmia, dysgraphia, Parkinsonism                                                                                                                                                                                                         |
| <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                                                   | Vision loss, keratitis, 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, Congestive heart failure                                              |
| Rare                                                   | QT prolongation, sinus tachycardia, sinus arrhythmia                                                                                       |
| <b>Vascular disorders</b>                              |                                                                                                                                            |
| Uncommon                                               | Flushing, hot flushes, hypotension, hypertension, peripheral coldness                                                                      |
| <b>Respiratory, thoracic and mediastinal disorders</b> |                                                                                                                                            |
| Uncommon                                               | Dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness                                                             |
| Rare                                                   | Pulmonary oedema, throat tightness                                                                                                         |
| Not known                                              | Respiratory depression                                                                                                                     |
| <b>Gastrointestinal disorders</b>                      |                                                                                                                                            |
| Common                                                 | Vomiting, nausea, dry mouth, constipation, diarrhoea, flatulence, abdominal distension                                                     |
| Uncommon                                               | Gastrooesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral                                                              |
| Rare                                                   | Ascites, pancreatitis, dysphagia, Swollen tongue                                                                                           |
| <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, hyperhidrosis, urticaria, pruritus                                                                                           |
| Rare                                                   | Stevens Johnson syndrome, cold sweat, Toxic Epidermal Necrolysis                                                                           |
| <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, urinary retention                                                                                                                          |
| <b>Reproductive system and breast disorders</b>             |                                                                                                                                                                     |
| Common                                                      | Erectile dysfunction                                                                                                                                                |
| Uncommon                                                    | Ejaculation delayed, sexual dysfunction, dysmenorrhoea, breast pain                                                                                                 |
| Rare                                                        | Amenorrhoea, breast discharge, breast enlargement, gynaecomastia                                                                                                    |
| <b>General disorders and administration site conditions</b> |                                                                                                                                                                     |
| Common                                                      | Gait abnormal, feeling drunk, fatigue, oedema peripheral, oedema, fall, feeling abnormal                                                                            |
| Uncommon                                                    | Generalised oedema, pyrexia, face oedema, chest tightness, pain, thirst, chills, asthenia                                                                           |
| <b>Investigations</b>                                       |                                                                                                                                                                     |
| Common                                                      | Weight increased                                                                                                                                                    |
| Uncommon                                                    | Blood creatine phosphokinase increased, blood glucose increased, platelet count decreased, blood creatinine increased, blood potassium decreased, weight decreased. |
| Rare                                                        | White blood cell count decreased                                                                                                                                    |

After discontinuation of short-term and long-term treatment with pregabalin withdrawal symptoms have been observed in some patients. The following reactions have been mentioned: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, convulsions, nervousness, depression, pain, hyperhidrosis and dizziness. 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.

#### **Reporting of suspected adverse reactions:**

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

#### **4.9 Overdose**

In the post-marketing experience, the most commonly reported adverse reactions observed when pregabalin was taken in overdose included somnolence, confusional state, agitation, and restlessness.

In rare occasions, cases of coma have been reported.

Treatment of pregabalin overdose should include general supportive measures and may include haemodialysis if necessary.

## **5. Pharmacological Properties**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group and ATC code: Pharmacotherapeutic group: Antiepileptics,

other antiepileptics 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 regimens 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 twice a day dosing (BID) or three times a day (TID) dosing. Overall, the safety and efficacy profiles for BID and TID dosing regimens were similar. A reduction in seizure frequency was observed by Week 1.

#### Monotherapy (newly diagnosed patients)

Pregabalin has been studied in 1 controlled clinical trial of 56-week duration with twice a day dosing (BID). 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 months 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 funduscopy examination) was conducted in over 3600 patients within controlled clinical trials. In these patients, visual acuity 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.

Funduscopy changes were observed in 1.7% of pregabalin-treated 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.

#### 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.

#### Hepatic impairment

No specific pharmacokinetic studies were carried out in patients with impaired liver function. Since pregabalin does not undergo significant metabolism and is excreted predominantly as unchanged drug in the urine, impaired liver function would not be expected to significantly alter pregabalin plasma concentrations.

#### Elderly (over 65 years of age)

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

### **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 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**

Microcrystalline Cellulose powder  
Hydroxypropylmethylcellulose (Hypromellose) K-100 M Maize starch  
Polyvinyl  
Polypyrrolidone K-9  
Purified Talcum  
Colloidal Anhydrous Silica (Aerosil)  
Magnesium Stearate  
Hydroxypropylmethylcellulose (Hypromellose)  
K-100 M Purified Talcum  
Colloidal Anhydrous Silica (Aerosil)  
Magnesium Stearate  
EHG Capsules '2' Light blue/ Light blue

### **6.2 Incompatibilities**

None reported from clinical studies

### **6.3 Shelf life**

36 months.

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

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

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

1 Alu-Alu pack of 10 Capsules each, packed in a primary carton along with the Pack Insert.

### **6.6 Special precautions for disposal and other handling**

No special requirement

## **7.0 MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESSES**

### **Marketing Authorization Holder:**

Company Name: THEON PHARMACEUTICALS LTD

Address: 400, Industrial Area, Phase-I, Panchkula-134113, Haryana, Country: India.

Telephone: +91 172 5210200, 5011077, 5033850

Telefax: +91 172 5033851

Manufacturing Site Address:

Company Name: THEON PHARMACEUTICALS LTD

Address: 400, Industrial Area, Phase-I, Panchkula-134113, Haryana Country: India

Telephone: +91 172 5210200, 5011077, 5033850

Telefax: +91 172 5033851

## **8.0 MARKETING AUTHORIZATION NUMBER**

CTD3199

## **9.0 DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION**

18th March 2016

## **10.0 DATE OF REVISION OF THE TEXT**

18th March 2016

## **11.0 DOSIMETRY**

Not applicable

## **12.0 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS**

Not applicable