Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

NEUROZIM 75 (Pregabalin Capsules 75 mg)

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

Hard Gelatin capsules
Pink/white, size `4` hard gelatin capsule filled with white to off- White powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Neuropathic pain
Pregabalin Capsules 75 mg is indicated for the treatment of peripheral and central neuropathic pain in adults.

Epilepsy
Pregabalin Capsules 75 mg is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalization.

Generalized anxiety disorder
Pregabalin Capsules 75 mg is indicated for the treatment of Generalized 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.

Generalized 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 ofPregabalin
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).

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..), as indicated in Table **1** determined using the following formula:

$$\frac{CL(mllmm) = [l.23\ x\ [140 - age\ (years)\ ]\ x\ weight\ (kg)\ ]}{\textbf{serum creatinine}\ (\mu\textbf{mol/1}} (\ x\ 0.85\ for\ female\ patie$$

Pregabalin is removed effectively from plasma by hemodialysis (50% of drug in 4 hours). For patients receiving hemodialysis, 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 hemodialysis treatment (see Table1).

Table 1. Pregabalin Dose Adjustment Based on Renal Function

Creatinine clearance (Cal cry) (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 hemodialysis (mg)			
	25	100	Single dose +

TIO 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 5.2).

Pediatric population

The safety and efficacy of Pregabalin Capsules 75 mg 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 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

Pregabalin Capsules 75 mg may be taken with or without food. Pregabalin Capsules 75 mg 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 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.

Severe cutaneous adverse reactions (SCARs)

SCARs including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported rarely in association with pregabalin treatment. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, pregabalin should be withdrawn immediately and an alternative treatment considered (as 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 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 5.1).
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.

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 4.2).

Suicidal ideation and behavior
Suicidal ideation and behavior 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 behavior. The mechanism of this risk is not known. Cases of suicidal ideation and behavior have been observed in patients treated with pregabalin in the post marketing experience (see section 4.8). An epidemiological study using a self-controlled study design (comparing treatment periods with non-treatment periods within an individual) showed evidence of an increased risk of new onset of suicidal behavior and death by suicide in patients treated with

pregabalin.
Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behavior emerge. Patients should be monitored for signs of suicidal ideation and behavior and appropriate treatment should be considered. Discontinuation of pregabalin treatment should be considered in case of suicidal ideation and behavior.

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 4.5). Ina 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 [or], 1.68 [95% CI, 1.19 -2.36]). This increased risk was observed at low doses of pregabalin (: S 300 mg, or 1.52 [95% CI, 1.04 -2.22]) and there was a trend for a greater risk at high doses of pregabalin (> 300 mg, or 2.51 [95% CI 1.24 -5.06]).

Misuse. Abuse potential or dependence
Pregabalin can cause drug dependence, which may occur at therapeutic doses. Cases of abuse and misuse have been reported. Patients with a history of substance abuse may be at higher risk for pregabalin misuse, abuse and dependence, and pregabalin should be used with caution in such patients. Before prescribing pregabalin, the patient's risk of misuse, abuse or dependence should be carefully evaluated.
Patients treated with pregabalin should be monitored for symptoms of pregabalin misuse, abuse or dependence, such as development of tolerance, dose escalation and drug-seeking behavior.

Withdrawal symptoms
After discontinuation of short-term and long-term treatment with pregabalin, withdrawal symptoms have been observed. The following symptoms have been reported: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, nervousness, depression, pain, convulsion, hyperhidrosis and dizziness. The occurrence of withdrawal symptoms following discontinuation of pregabalin may indicate drug dependence (see section 4.8). The patient should be informed about this at the start of the treatment. If pregabalin should be discontinued, it is recommended this should be done gradually over a minimum of 1week independent of the indication (see section 4.2).

Convulsions, including status epileptics 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.

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

Women of childbearing potential/Contraception
Pregabalin Capsules 75 mg 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
Pregabalin Capsules 75 mg 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.

Sodium content
Pregabalin Capsules 75 mg contains less than I mmol sodium (23 mg) per hard capsule. Patients on low sodium diets can be informed that this medicinal product is essentially 'sodium-free'.

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 postrnarketing 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

Women of childbearing potential/Contraception
Women of childbearing potential have to use effective contraception during treatment (see section 4.4).

Pregnancy
Studies in animals have shown reproductive toxicity (see section 5.3).

Pregabalin has been shown to cross the placenta in rats (see section 5.2). Pregabalin may cross the human placenta.

Major congenital malformations
Data from a Nordic observational study of more than 2700 pregnancies exposed to pregabalin in the first trimester showed a higher prevalence of major congenital malformations (MCM) among the pediatric population (live or stillborn) exposed to pregabalin compared to the unexposed population (5.9% vs. 4.1%).

The risk of MCM among the pediatric population exposed to pregabalin in the first trimester was slightly higher compared to unexposed population (adjusted prevalence ratio and 95% confidence interval: 1.14 (0.96-1.35)), and compared to population exposed to lamotrigine (1.29 (1.01-1.65)) or to duloxetine (1.39 (1.07-1.82)).
The analyses on specific malformations showed higher risks for malformations of the nervous system, the eye, orofacial clefts, urinary malformations and genital malformations, but numbers were small and estimates imprecise.

Pregabalin Capsules 75 mg 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

Pregabalin Capsules 75 mg may have minor or moderate influence on the ability to drive and use machines. Pregabalin Capsules 75 mg 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 programmed 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 G". 1/10); common G". 1/100 to < 1/10); uncommon ("': 1/1,000 to < 1/100); rare ("': 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The adverse reactions listed may also be associated with the underlying disease and/or concomitant medicinal products.
In the treatment of central neuropathic pain due to spinal cord injury the incidence of adverse reactions in general, CNS adverse reactions and especially somnolence was increased (see section 4.4).
Additional reactions reported from post marketing experience are included in italics in the list below. Table 2. Pregabalin Adverse Drug Reactions

System Organ Class	**Adverse Drug reaction**
Infections and Infestations Common	Nasopharyngitis
Blood and lymphatic system disorders Uncommon	Neutropenia
Immune system disorders Uncommon	Hypersensitivity

Rare	Angioedema, allergic reaction
Metabolism and nutrition disorders Common Uncommon	 Appetite increased Anorexia, hypoglycaemia
Psychiatric disorder Common Uncommon Rare Not known	 Euphoric mood, confusion, irritability, disorientation, insomnia, libido decreased Hallucination, panic attack, restlessness, agitation, depression, depressed mood, elevated mood, aggression, mood swings, depersonalization, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy Disinhibition, suicidal behavior, Suicidal ideation Drug dependence
Nervous system disorder Very common Common Uncommon Rare	 Dizziness, somnolescence, headache Ataxia, coordination abnormal, tremor, dysarthria, amnesia, memory impairment, disturbance in attention, paraesthesia, hypoaesthesia, sedation, balance disorder, lethargy 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 Convulsions, parosmia, hypokinesia, dysgraphia, parkinsonism
Eye disorder Common Uncommon Rare	 Vision blurred, diplopia Peripheral vision loss, visual disturbance, eye swelling, visual field defect, visual acuity reduced, eye pain, asthenopia, photopsia, dry eye, lacrimation increased, eye irritation Vision loss, keratitis, oscillopsia, altered visual depth perception, mydriasis, strabismus, visual brightness
Ear & Labyrinth disorders Common Uncommon	 Vertigo Hyperacusis
Cardiac disorder	

Uncommon Rare	Tachycardia, atrioventricular block first degree, sinus bradycardia, congestive heart failure QT prolongation, sinus tachycardia, sinus arrhythmia
Respiratory, thoracic & Mediastinal disorder Uncommon Rare Not known	 Dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness Pulmonary oedema, throat tightness Respiratory depression
Gastrointestinal disorders Common Uncommon Rare	 Vomiting, nausea, constipation, diarrhoea, flatulence, abdominal distension, dry mouth Gastro esophageal reflux disease, salivary hyper secretion, hypoaesthesia oral Ascites, pancreatitis, swollen tongue, dysphagia
Hepatobiliary disorders Uncommon Rare Very rare	 Elevated liver enzymes* Jaundice Hepatic failure, hepatitis
Skin and subcutaneous tissue disorders Uncommon Rare	 Rash papular, urticaria, hyperhidrosis, pruritus Toxic epidermal necrolysis, Stevens-Johnson syndrome, cold sweat
Musculoskeletal and connective tissue disorders Common Uncommon Rare	 Muscle cramp, arthralgia, back pain, pain in limb, cervical spasm Joint swelling, myalgia, muscle twitching, neck pain, muscle stiffness Rhabdomyolysis
Renal & urinary disorders Uncommon Rare	 Urinary incontinence, dysuria Renal failure, oliguria, urinary retention
Reproductive system & breast disorders Common Uncommon Rare	 Erectile dysfunction Sexual dysfunction, ejaculation delayed, dysmenorrhoea, breast pain Amenorrhoea, breast discharge, breast enlargement, gynaecomastia
General disorders & Administration site conditions Common	 Oedema peripheral, oedema, gait abnormal, fall, feeling drunk, feeling abnormal, fatigue Generalized oedema,face oedema, chest

Uncommon	tightness, pain, pyrexia, thirst, chills, asthenia
Investigation Common Uncommon Rare	 Weight increased Blood creatine phosphokinase increased, blood glucose increased, platelet count decreased, blood creatinine increased, blood potassium decreased, weight decreased White blood cell count decreased

• Alanine amiootransferase increased (ALn and aspartate amiootransferase increased (Asn.

After discontinuation of short-term and long-term treatment with pregabalin withdrawal symptoms have been observed. The following symptoms have been reported: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, convulsions, nervousness, depression, pain, hyperhidrosis and dizziness. These symptoms may indicate drug dependence. The patient should be informed about this at the start of the treatment. Concerning discontinuation of long-term treatment of pregabalin, data suggest that the incidence and severity of withdrawal symptoms may be dose-related (see sections 4.2 and 4.4).

Pediatric population

The pregabalin safety profile observed in five pediatric studies in patients with partial seizures with or without secondary generalization (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=l75; pharmacokinetic and tolerability study, n=65; and two 1year open label follow on safety studies, n=54 and n=43l) was similar to that observed in the adult studies of patients with epilepsy. The most common adverse events observed in the 12-week study with pregabalin treatment were somnolence, pyrexia, upper respiratory tract infection, increased appetite, weight increased, and nasopharyngitis.

The most common adverse events observed in the 14-day study with pregabalin treatment were somnolence, upper respiratory tract infection, and pyrexia (see sections 4.2, *5*.1 and 5.2).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 through www.zimlab.in .

4.9 Overdose

In the post marketing experience, the most commonly reported adverse reactions observed when pregabalin was taken in overdose included somnolence, confessional 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 hemodialysis if necessary (see section 42 Table 1).

5. PHARMACOLOGICAL PROPERTIES

5. L Pharmacodynamic properties

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

The active substance, pregabalin, is a gamma-aminobutyric acid analogue [(S)-3-aminomethy1)-5-methylhexanoic acid].

Mechanism of action

Pregabalin binds to an auxiliary subunit (a2- 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 (TIO) dosing. Overall, the safety and efficacy profiles for BID and TIO 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 patient's 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 TIO dosing. Overall, the safety and efficacy profiles for BID and TIO dosing regimens were similar.

A reduction in seizure frequency was observed by Week 1.

Pediatric population

The efficacy and safety of pregabalin as adjunctive treatment for epilepsy in

pediatric patients below the age of 12 and adolescents 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 (n65) with partial onset seizures were similar to those observed in adults. Results of a 12-week placebo-controlled study of 295 pediatric patients aged 4 to 16 years and a 14-day placebo-controlled study of 175 pediatric patients aged 1month to younger than 4 years of age performed to evaluate the efficacy and safety of pregabalin as adjunctive therapy for the treatment of partial onset seizures and two 1year open label safety studies in 54 and 431 pediatric patients respectively, 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 adult studies of patients with epilepsy (see sections 4.2, 4.8 and 5.2).

In the 12-week placebo-controlled study, pediatric patients (4 to 16 years of age) 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.

In the 14-day placebo-controlled study, pediatric patients (1 month to younger than 4 years of age) were assigned to pregabalin 7 mg/kg/day, pregabalin 14 mg/kg/day, or placebo. Median 24-hour seizure frequencies at baseline and at the final visit were 4.7 and 3.8 for pregabalin 7 mg/kg/day, 5.4 and 1.4 for pregabalin 14 mg/kg/day, and 2.9 and 2.3 for placebo, respectively. Pregabalin 14 mg/kg/day significantly reduced the log-transformed partial onset seizure frequency versus placebo (p=0.0223); pregabalin 7 mg/kg/day did not show improvement relative to placebo.

Ina 12-week placebo-controlled study in subjects with Primary Generalized Tonic-Clonic (PGTC) seizures 219 subjects (aged *5* to 65 years, of which 66 were aged 5 to 16 years) were assigned to pregabalin *5* mg/kg/day (maximum 300 mg/day), 10 mg/kg/day (maximum 600 mg/day) or placebo as adjunctive therapy. The percentage of subjects with at least a 50% reduction in PGTC seizure rate was 41.3%, 38.9% and 41.7% for pregabalin 5 mg/kg/day, pregabalin 10 mg/kg/day and placebo respectively.

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.

Generalized 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 funduscopic 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. Funduscopic 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 ≥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 Coax by approximately 25-30% and a delay in t, 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 lactating rats. In humans, the apparent volume of distribution of pregabalin following oral administration is approximately 0.56 I/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 racemization 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 hemodialysis 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 hemodialysis (following a 4 hour hemodialysis 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 hemodialysis 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.

Pediatric population
Pregabalin pharmacokinetics were evaluated in pediatric 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 pediatric 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 post dose.

Pregabalin Coax and AUC parameters increased in a linear manner with increasing dose within each age group. The AUC was lower by 30% in pediatric 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 pediatric 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 pediatric 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 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 an 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 hypo activity, hyperactivity and ataxia. An increased incidence of retinal atrophy commonly observed in aged albino rats was seen after long-term exposure to pregabalin at exposures *5* times the mean human exposure at the maximum recommended clinical dose.

Pregabalin was not teratogenic in mice, rats or rabbits. Fetal 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 tumors 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 tumors 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 tumor 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

Mannitol
Maize starch
Purified talc
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at a temperature not exceeding 30°C, protect from moisture.

6.5 Nature and contents of container

Alu- PVC blister pack of 3 x 10 capsules

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Zim Laboratories Limited.

Sadoday Gyan (Ground Floor),
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8. MARKETING AUTHORISATION NUMBER(S)

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