PREGABALIN
LYRICA
25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, and 300 mg Capsule

1.0 THERAPEUTIC CATEGORY

Alpha_2-Delta Ligand Modulator
(Anti-Neuropathic Pain/Anti-Convulsant)

2.0 FORMULATION

LYRICA 25 mg, capsule: Each capsule contains 25 mg pregabalin.
LYRICA 50 mg, capsule: Each capsule contains 50 mg pregabalin.
LYRICA 75 mg, capsule: Each capsule contains 75 mg pregabalin.
LYRICA 100 mg capsule: Each capsule contains 100mg pregabalin.
LYRICA 150 mg, capsule: Each capsule contains 150 mg pregabalin.
LYRICA 200 mg, capsule: Each capsule contains 200 mg pregabalin.
LYRICA 300 mg, capsule: Each capsule contains 300 mg pregabalin.

3.0 DESCRIPTION

Pregabalin is a gamma-aminobutyric acid (GABA) analogue (S)-3-(aminomethyl)-5-methylexaoic acid) with an empirical formula of C_8 H_{17} NO_2 and molecular weight of 159.23. The molecular structure of pregabalin is:

\[
\text{\includegraphics{pregabalin_structure.png}}
\]

4.0 CLINICAL PARTICULARS

4.1 Therapeutic indications

Neuropathic Pain

Pregabalin is indicated for the treatment of neuropathic pain in adults, including neuropathic pain associated with spinal cord injury.
Epilepsy

Pregabalin is indicated as adjunctive therapy in adults with partial seizures, with or without secondary generalization.

Fibromyalgia

Pregabalin is indicated for the management of fibromyalgia.

Generalized Anxiety Disorder

Pregabalin is indicated for the treatment of Generalized Anxiety Disorder (GAD) in adults.

4.2 Dosage and Method of Administration

The dose range is 150 to 600 mg per day given in either two or three divided doses.

Pregabalin may be taken with or without food.

Neuropathic Pain

Pregabalin treatment can be started at a dose of 150 mg per day. Based on individual patient response and tolerability, the dosage 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. Based on individual patient response and tolerability, the dosage may be increased to 300 mg per day after one week. The maximum dosage of 600 mg per day may be achieved after an additional week.

Fibromyalgia

The usual dose range for most patients is 300 to 450 mg per day given in two divided doses. Some patients may derive additional benefit at 600 mg per day. Dosing should begin at 75 mg two times a day (150 mg/day) and may be increased to 150 mg two times a day (300 mg/day) within one week based on efficacy and tolerability. Patients who do not experience sufficient benefit with 300 mg/day may be further increased to 225 mg
two times a day (450 mg/day). If needed, in some patients, based on individual response and tolerability, the dose may be increased to maximum dosage of 600 mg/day 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 dosage may be increased to 300 mg per day after 1 week. Following an additional week the dosage may be increased to 450 mg per day. The maximum dosage of 600 mg per day may be achieved after an additional week.

**Discontinuation of Pregabalin**

If pregabalin has to be discontinued it is recommended that this should be done gradually over a minimum of one week.

**Patients with renal impairment**

Dosage reduction in patients with compromised renal function must be individualized according to creatinine clearance (CLcr), (see section 5.2 Pharmacokinetic Properties, Pharmacokinetic in Special Patient Groups, Renal Impairment), as indicated in Table 1 determined using the following formula:

\[
CLcr(\text{ml/min}) = \frac{[140 - \text{age(years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85 \text{ for female patients}
\]

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 Table 1).

**Table 1. Pregabalin Dosage Adjustment Based on Renal Function**

<table>
<thead>
<tr>
<th>Creatinine Clearance (CLcr) (mL/min)</th>
<th>Total Pregabalin Daily Dose*</th>
<th>Dose Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥60</td>
<td>Starting dose (mg/day)</td>
<td>Maximum dose (mg/day)</td>
</tr>
<tr>
<td></td>
<td>150</td>
<td>600</td>
</tr>
</tbody>
</table>
Use in Patients with Hepatic Impairment

No dosage adjustment is required for patients with hepatic impairment (see section 5.2 Pharmacokinetic Properties, Pharmacokinetic in Special Patient Groups, Hepatic Impairment).

Use in Children and Adolescents (12 to 17 years of age)

The safety and effectiveness of Pregabalin in pediatric patients below the age of 12 years and adolescents has not been established.

The use in children is not recommended (see section 5.3 Preclinical safety data).

Use in the Elderly (over 65 years of age)

Elderly patients may require a dose reduction of pregabalin due to a decreased renal function (see section 5.2 Pharmacokinetic Properties, Pharmacokinetics in Special Patient Groups, Elderly (over 65 years of age)).

4.3 Contraindications

Hypersensitivity to the active substance.

4.4 Special Warnings and Special Precautions for Use

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Some diabetic patients who gain weight on pregabalin treatment may need to adjust hypoglycemic medications.

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.

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 medication.

In the postmarketing experience, transient visual blurring and other changes in visual acuity have been reported in patients treated with pregabalin. Discontinuation of pregabalin may result in resolution or improvement of these visual symptoms.

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.

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, hyperhidrosis and diarrhea

Pregabalin is not known to be active at receptor sites associated with drugs of abuse. Cases of abuse have been reported in the post-marketing database. As with any CNS active drug, carefully evaluate patients for history of drug abuse and observe them for signs of pregabalin abuse.

Although the effects of discontinuation on the reversibility of renal failure have not been systematically studied, improved renal function following discontinuation or dose reduction of pregabalin has been reported.

Although there has been no causal relationship identified between exposure to pregabalin and congestive heart failure, there have been post-marketing reports of congestive heart failure in some patients receiving pregabalin. In short-term trials of patients without clinically significant heart or peripheral vascular disease, there was no apparent association between peripheral edema and cardiovascular complications such as hypertension or congestive heart failure. Because there are limited data on
severe congestive heart failure patients, pregabalin should be used with caution in these patients (See Section 4.8 Undesirable Effects).

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 \textit{in vitro}, and is not bound to plasma proteins, it is unlikely to produce, or be subject to, pharmacokinetic interactions.

Accordingly, in \textit{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.

Co-administration of pregabalin with the oral contraceptives norethisterone and/or ethinyl estradiol does not influence the steady-state pharmacokinetics of either substance. 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. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone.

In the post-marketing experience, there are reports of respiratory failure and coma in patients taking pregabalin and other CNS depressant medications. There are post-marketing reports of events related to reduced lower gastrointestinal tract function (eg intestinal obstruction, paralytic ileus, constipation) when pregabalin was co-administered with medications that have the potential to produce constipation, such as opioid analgesics.

No specific pharmacodynamic interaction studies were conducted in elderly volunteers.

4.6 Fertility, Pregnancy and Lactation

Pregnancy

There are no adequate data on the use of Pregabalin in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3 Preclinical safety data). The potential risk to humans is unknown.
Therefore, pregabalin should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the fetus. Effective contraception must be used in women of child bearing potential.

Lactation

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.

4.7 Effects on Ability to Drive and Use Machines

Pregabalin may cause dizziness and somnolence and therefore may influence the ability to drive or use machines. Patients are advised not to drive, operate complex machinery or engage in other potentially hazardous activities until it is known whether this medication affects their ability to perform these activities.

4.8 Undesirable Effects

The pregabalin clinical program involved over 12,000 patients who were exposed to pregabalin, of whom over 7000 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 events was 14% 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.

Select adverse events that were treatment related in the pooled analysis of clinical trials are listed in the table below by system organ class and frequency (very common (≥1/10), common (≥ 1/100, <1/10), uncommon (≥1/1000, <1/100) and rare (<1/1000).

The adverse reactions listed may also be associated with the underlying disease and concomitant medications.

Table 2 – Adverse Events from Clinical Trial Experience

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse drug reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and Infestations</td>
<td>Nasopharyngitis</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Neutropenia</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
</tr>
<tr>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
</tr>
<tr>
<td>Category</td>
<td>Condition</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Common</td>
<td>Appetite increased</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Anorexia</td>
</tr>
<tr>
<td>Rare</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Confusion, disorientation, irritability, euphoric mood, libido decreased,</td>
</tr>
<tr>
<td>Uncommon</td>
<td>insomnia</td>
</tr>
<tr>
<td>Rare</td>
<td>Depersonalization, anorgasmia, restlessness, depression, agitation, mood</td>
</tr>
<tr>
<td></td>
<td>swings, depressed mood, word finding difficulty, hallucination, abnormal</td>
</tr>
<tr>
<td></td>
<td>dreams, libido increased, panic attack, apathy</td>
</tr>
<tr>
<td>Rare</td>
<td>Disinhibition, elevated mood</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Very Common</td>
<td>Dizziness, somnolence</td>
</tr>
<tr>
<td>Common</td>
<td>Ataxia, coordination abnormal, balance disorder, amnesia, disturbance in</td>
</tr>
<tr>
<td></td>
<td>attention, memory impairment, tremor, dysarthria, paresthesia, sedation,</td>
</tr>
<tr>
<td></td>
<td>lethargy</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Cognitive disorder, hypoesthesia, nystagmus, speech disorder, myoclonus,</td>
</tr>
<tr>
<td></td>
<td>hyporeflexia, dyskinesia, psychomotor hyperactivity, dizziness postural,</td>
</tr>
<tr>
<td></td>
<td>hyperaesthesia, ageusia, burning sensation, intention tremor, stupor,</td>
</tr>
<tr>
<td></td>
<td>syncope</td>
</tr>
<tr>
<td>Rare</td>
<td>Hypokinesia, parosmia, dysgraphia</td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Vision blurred, diplopia</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Visual disturbance, visual field defect, dry eye, eye swelling, visual</td>
</tr>
<tr>
<td></td>
<td>acuity reduced, eye pain, asthenopia, lacrimation increased</td>
</tr>
<tr>
<td>Rare</td>
<td>Photopsia, eye irritation, mydriasis, oscillopsia, altered visual depth</td>
</tr>
<tr>
<td></td>
<td>perception, peripheral vision loss, strabismus, visual brightness</td>
</tr>
<tr>
<td><strong>Ear and labyrinth disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Vertigo</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Hyperacusis</td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Atrioventricular block first degree, tachycardia</td>
</tr>
<tr>
<td>Rare</td>
<td>Sinus tachycardia, sinus arrhythmia, sinus bradycardia</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Hypotension, hypertension, flushing, hot flushes, peripheral coldness</td>
</tr>
<tr>
<td>**Respiratory, thoracic and</td>
<td></td>
</tr>
<tr>
<td>mediastinal disorders**</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Dyspnea, cough, nasal dryness</td>
</tr>
<tr>
<td>Rare</td>
<td>Nasal congestion, epistaxis, rhinitis, snoring, throat tightness</td>
</tr>
</tbody>
</table>

**Gastrointestinal disorders**
- **Common**: Vomiting, abdominal distension, constipation, dry mouth, flatulence
- **Uncommon**: Salivary hypersecretion, gastroesophageal reflux disease, hypoesthesia oral
- **Rare**: Ascites, dysphagia, pancreatitis

**Skin and subcutaneous tissue disorders**
- **Uncommon**: Sweating, rash papular
- **Rare**: Cold sweat, urticaria

**Musculoskeletal and connective tissue disorders**
- **Uncommon**: Muscle twitching, joint swelling, muscle cramp, myalgia, arthralgia, back pain, pain in limb, muscle stiffness
- **Rare**: Cervical spasm, neck pain, rhabdomyolysis

**Renal and urinary disorders**
- **Uncommon**: Dysuria, urinary incontinence
- **Rare**: Oliguria, renal failure

**Reproductive system and breast disorders**
- **Common**: Erectile dysfunction
- **Uncommon**: Ejaculation delayed, sexual dysfunction
- **Rare**: Amenorrhea, breast pain, breast discharge, dysmenorrhea, breast enlargement

**General disorders and administration site conditions**
- **Common**: Peripheral edema, edema, gait abnormal, feeling drunk, fatigue
- **Uncommon**: Chest tightness, fall, generalized edema, pain, chills, asthenia, thirst
- **Rare**: Pyrexia

**Investigations**
- **Common**: Weight increase
- **Uncommon**: Alanine aminotransferase increased, blood creatine phosphokinase increased, aspartate aminotransferase increased, platelet count decreased.
- **Rare**: Blood glucose increased, blood creatinine increased, blood potassium decreased, weight decreased, white blood cell count decreased

The following adverse events were reported during POST-MARKETING SURVEILLANCE.
Immune System Disorder: Angioedema, Allergic reaction, Hypersensitivity

Nervous System Disorders: Headache, loss of consciousness, mental impairment

Cardiac Disorders: Congestive heart failure

Eye disorders: Keratitis

Gastrointestinal Disorders: Swollen tongue, diarrhea, nausea

Reproductive system and breast disorders: Gynecomastia

General disorders and administration site conditions: Malaise

Skin and Subcutaneous Tissue Disorders: Face swelling, Pruritus

Renal and Urinary Disorders: Urinary Retention

Respiratory and Thoracic Disorders: Pulmonary edema

4.9 Overdose

In overdoses up to 15 g, no unexpected adverse reactions were reported.

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

Treatment of pregabalin overdose should include general supportive measures and may include haemodialysis if necessary (see section 4.2 Dosage and Method of Administration Table 1)

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 (2-δ protein) of voltage-gated calcium channels in the central nervous system.

Evidence from animal models with nerve damage has shown that pregabalin reduces calcium dependent release of pro-nociceptive neurotransmitters in the spinal cord possibly by disrupting calcium trafficking and/or reducing calcium currents. Evidence from other animal models of nerve damage suggest the antinociceptive activities of pregabalin may also be mediated through interactions with the descending noradrenergic and serotonergic pathways.

Clinical Experience

Neuropathic Pain

Efficacy has been shown in studies in diabetic neuropathy and post herpetic neuralgia. Efficacy has not been studied in other models of neuropathic pain.

Pregabalin has been studied in 9 controlled clinical studies of up to 13 weeks with twice a day dosing and up to 8 weeks with three times a day dosing. Overall, the safety and efficacy profiles for twice a day and three times a day dosing regimens were similar.

In clinical trials up to 13 weeks, a reduction in pain was seen by week 1 and was maintained throughout the treatment period.

In controlled clinical trials 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.

Fibromyalgia

Pregabalin as monotherapy has been studied in 5 placebo-controlled studies, three of 12 weeks fixed dose duration, one of 7 weeks fixed dose duration and a 6 month study demonstrating long term efficacy. Pregabalin treatment in all fixed dose studies produced a significant reduction in pain associated with fibromyalgia at doses from 300 to 600 mg/day (BID).

In the three 12 week fixed dose studies, 40% of pregabalin treated patients experienced a 30% or more improvement in pain score versus 28% of the patients on placebo; 23% of treated patients experienced a 50% or more improvement in pain score versus 15% of the patients on placebo.
Pregabalin produced significantly superior global assessment scores via the Patient Global Impression of Change (PGIC) in the three 12 week fixed dose studies as compared to placebo treatment (41% patients feeling very much or much improved on pregabalin versus 29% on placebo). As measured by Fibromyalgia Impact Questionnaire, (FIQ), pregabalin produced a statistically significant improvement in function versus placebo treatment in 2 out of the 3 fixed dose studies in which it was evaluated.

Pregabalin treatment produced significant improvements in patient reported sleep outcomes in the 4 fixed dose studies as measured by MOS-SS Sleep disturbance subscale (Medical Outcomes Study Sleep Scale), MOS-SS overall sleep problem index, and the daily sleep quality diary.

In the 6 month study, improvement in pain, global assessment (PGIC), function (FIQ total score) and sleep (MOS-SS Sleep disturbance subscale) were maintained for pregabalin treated patients for a significantly longer period compared to placebo.

Pregabalin 600 mg/day showed an additional improvement in patient reported sleep outcomes as compared to 300 and 450 mg/day; mean effects on pain, global assessment, and FIQ were similar at 450 and 600 mg/day, although the 600mg per day dose was less well tolerated.

**Epilepsy**

Pregabalin has been studied in 3 controlled clinical studies of 12 week duration with either twice a day dosing or three times a day dosing. Overall, the safety and efficacy profiles for twice a day and three times a day dosing regimens were similar.

A reduction in seizure frequency was observed by Week 1.

**Generalized Anxiety Disorder**

Pregabalin has been studied in 6 controlled studies of 4 to 6 weeks duration, an elderly study of 8 weeks 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 weeks 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.
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 Cmax by approximately 25-30% and a delay in tmax 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 readily 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.

Metabolism:

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 Pharmacokinetic Properties, Pharmacokinetic in Special Patient Groups, Renal impairment).
Dosage adjustment in patients with reduced renal function or undergoing hemodialysis is necessary (see section 4.2 Dosage and Method of Administration, Table 1).

**Linearity / non-linearity:**

Pregabalin pharmacokinetics are linear over the recommended daily dose range. Inter-subject pharmacokinetic variability for pregabalin is low (<20%). Multiple dose pharmacokinetics are predictable from single-dose data. Therefore, there is no need for routine monitoring of plasma concentrations of pregabalin.

**Pharmacokinetics in Special Patient Groups**

**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, dosage reduction in patients with renal impairment and dosage supplementation following hemodialysis is necessary (see section 4.2 Dosage and Method of Administration, Table 1).

**Hepatic impairment**

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

**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 (see section 4.2 Dosage and Method of Administration, Table 1).

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.

Teratogenicity:

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 $\geq 2$ times the maximum recommended human exposure.

Mutagenicity:

Pregabalin is not genotoxic based on results of a battery of in vitro and in vivo tests.

Carcinogenicity:

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 hemangiosarcoma 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 estrous cycle were observed at 5-fold the human therapeutic exposure. Neurobehavioral/cognitive effects
were observed in juvenile rats 1-2 weeks after exposure >2 times (acoustic startle response) or >5 times (learning/memory) 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 Shelf life

Please see outer package for the expiry date of the product.

6.2 Storage

Store at temperatures not exceeding 30°C

6.3 Instructions for use and handling

No special requirements.

6.4 Availability

25 mg capsule: White hard gelatin capsules, marked “Pfizer” on the cap and “PGN 25” on the body with black ink. Available in blister packs of 14’s in boxes of 56’s.

50 mg capsule: White hard gelatin capsules, marked “Pfizer” on the cap and “PGN 50” on the body with black ink. The body is also marked with a black band. Available in blister packs of 14’s in boxes of 56’s.

75 mg capsule: White and orange hard gelatin capsules marked “Pfizer” on the cap and “PGN 75” on the body with black ink. Available in blister packs of 14’s in boxes of 56’s.

100 mg capsule: White and orange hard gelatin capsules marked “Pfizer” on cap and “PGN 100” on the body with black ink. Available in blister packs of 21’s in boxes of 84’s.

150 mg capsule: White hard gelatin capsules marked “Pfizer” on the cap and “PGN 150” on the body with black ink. Available in blister packs of 14’s in boxes of 56’s.

200 mg capsule: Light orange opaque hard gelatin capsules marked “Pfizer” on the cap and “PGN 200” on the body with black ink. Available in blister packs of 21’s in boxes of 84’s.
300 mg capsule: White and orange hard gelatin capsules marked “Pfizer” on the cap and “PGN 300” on the body with black ink. Available in blister packs of 14’s in boxes of 56’s.

**CAUTION:** Food, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Manufactured by: Pfizer Manufacturing Deutschland GmbH- Betriebsstätte Freiburg Mooswaldallee 1 79090 Freiburg, Germany

Imported by: Pfizer, Inc.
23/F Ayala Life-FGU Center
6811 Ayala Avenue, Makati City
Philippines

<table>
<thead>
<tr>
<th>Revision No.</th>
<th>Revision Date</th>
<th>Reference</th>
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