ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT

Pregabalin Sandoz 25 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 25 mg of pregabalin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.
Pale yellow-brown opaque cap and body, capsule size 4 (14.3 mm x 5.3 mm), filled with white to nearly white coloured powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Epilepsy
Pregabalin Sandoz is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.

Generalised Anxiety Disorder
Pregabalin Sandoz 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 individualised according to creatinine clearance (CLcr), as indicated in Table 1 determined using the following formula:

\[
CL_c = \frac{1.23 \times \left[ 140 \cdot \text{age (years)} \right] \times \text{weight (kg)}}{\text{serum creatinine (µmol/L)}} \times \frac{0.85}{\text{for female patients}}
\]

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**

<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></td>
<td>Starting dose (mg/day)</td>
<td>Maximum dose (mg/day)</td>
</tr>
<tr>
<td>≥ 60</td>
<td>150</td>
<td>600 BID or TID</td>
</tr>
<tr>
<td>≥ 30 - &lt; 60</td>
<td>75</td>
<td>300 BID or TID</td>
</tr>
<tr>
<td>≥ 15 - &lt; 30</td>
<td>25 – 50</td>
<td>150 Once Daily or BID</td>
</tr>
<tr>
<td>&lt; 15</td>
<td>25</td>
<td>75 Once Daily</td>
</tr>
<tr>
<td>Supplementary dosage following haemodialysis (mg)</td>
<td>25</td>
<td>100 Single dose +</td>
</tr>
</tbody>
</table>

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 (see section 5.2).

*Paediatric population*
The safety and efficacy of pregabalin in children below the age of 12 years and in adolescents (12-17 years of age) have not been established. Currently available data are described in section 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

*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**
Pregabalin Sandoz may be taken with or without food.
Pregabalin Sandoz is for oral use only.

### 4.3 Contraindications

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

### 4.4 Special warnings and precautions for use

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

**Hypersensitivity reactions**
There have been reports in the postmarketing experience of hypersensitivity reactions, including cases of angioedema. Pregabalin should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper 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 postmarketing reports of loss of consciousness, confusion and mental impairment. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medicinal product.

**Vision-related effects**
In controlled trials, a higher proportion of patients treated with pregabalin reported blurred vision than did patients treated with placebo which resolved in a majority of cases with continued dosing. In the clinical studies 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 postmarketing experience, visual adverse reactions have also been reported, including loss of vision, visual blurring or other changes of visual acuity, many of which were transient. Discontinuation of pregabalin may result in resolution or improvement of these visual symptoms.

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

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

**Withdrawal symptoms**
After discontinuation of short-term and long-term treatment with pregabalin, withdrawal symptoms have been observed in some patients. The following events have been mentioned: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, nervousness, depression, pain, convulsion, hyperhidrosis and dizziness, suggestive of physical dependence. The patient should be informed about this at the start of the treatment.

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

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

**Congestive heart failure**

There have been postmarketing reports of congestive heart failure in some patients receiving pregabalin. These reactions are mostly seen in elderly cardiovascular compromised patients during pregabalin treatment for a neuropathic indication. Pregabalin should be used with caution in these patients. Discontinuation of pregabalin may resolve the reaction.

**Treatment of central 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 postmarketing reports of events related to reduced lower gastrointestinal tract function (e.g. intestinal obstruction, paralytic ileus, constipation) when pregabalin was co-administered with medications that have the potential to produce constipation, such as opioid analgesics. When pregabalin and opioids will be used in combination, measures to prevent constipation may be considered (especially in female patients and elderly).

**Misuse, abuse potential or dependence**

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

**Encephalopathy**

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

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

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

**Pregnancy**

There are no adequate data from the use of pregabalin in pregnant women.

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

Pregabalin Sandoz 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 Sandoz may have minor or moderate influence on the ability to drive and use machines. Pregabalin Sandoz 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 program involved over 8900 patients 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 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 (≥ 1/10); common (≥ 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 postmarketing experience are included in italics in the list below.

Table 2. Pregabalin Adverse Drug Reactions

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse drug reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Nasopharyngitis</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Neutropaenia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Rare</td>
<td>Angioedema, allergic reaction</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Appetite increased</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Anorexia, hypoglycaemia</td>
</tr>
</tbody>
</table>
### Psychiatric disorders

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Euphoric mood, confusion, irritability, disorientation, insomnia, libido decreased</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Hallucination, panic attack, restlessness, agitation, depression, depressed mood, elevated mood, <strong>agression</strong>, mood swings, depersonalisation, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy</td>
</tr>
<tr>
<td>Rare</td>
<td>Disinhibition</td>
</tr>
</tbody>
</table>

### Nervous system disorders

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Common</td>
<td>Dizziness, somnolence, headache</td>
</tr>
<tr>
<td>Common</td>
<td>Ataxia, coordination abnormal, tremor, dysarthria, amnesia, memory impairment, disturbance in attention, paraesthesia, hypoaesthesia, sedation, balance disorder, lethargy</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Syncope, stupor, myoclonus, <strong>loss of consciousness</strong>, psychomotor hyperactivity, dyskinesia, dizziness postural, intention tremor, nystagmus, cognitive disorder, mental impairment, speech disorder, hyporeflexia, hyperaesthesia, burning sensation, ageusia, malaise</td>
</tr>
<tr>
<td>Rare</td>
<td><strong>Convulsions</strong>, parosmia, hypokinesia, dysgraphia</td>
</tr>
</tbody>
</table>

### Eye disorders

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Vision blurred, diplopia</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Peripheral vision loss, visual disturbance, eye swelling, visual field defect, visual acuity reduced, eye pain, asthenopia, photopsia, dry eye, lacerimation increased, eye irritation</td>
</tr>
<tr>
<td>Rare</td>
<td><strong>Vision loss, keratitis</strong>, oscillopsia, altered visual depth perception, mydriasis, strabismus, visual brightness</td>
</tr>
</tbody>
</table>

### Ear and labyrinth disorders

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Vertigo</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Hyperacusis</td>
</tr>
</tbody>
</table>

### Cardiac disorders

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Tachycardia, atrioventricular block first degree, sinus bradycardia, <strong>congestive heart failure</strong></td>
</tr>
<tr>
<td>Rare</td>
<td><strong>QT prolongation</strong>, sinus tachycardia, sinus arrhythmia</td>
</tr>
</tbody>
</table>

### Vascular disorders

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Hypotension, hypertension, hot flushes, flushing, peripheral coldness</td>
</tr>
</tbody>
</table>

### Respiratory, thoracic and mediastinal disorders

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness</td>
</tr>
<tr>
<td>Rare</td>
<td><strong>Pulmonary oedema</strong>, throat tightness,</td>
</tr>
</tbody>
</table>

### Gastrointestinal disorders

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Vomiting, <strong>nausea</strong>, constipation, <strong>diarrhoea</strong>, flatulence, abdominal</td>
</tr>
<tr>
<td>Common</td>
<td>distension, dry mouth</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Gastrooesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Ascites, pancreatitis, <em>swollen tongue</em>, dysphagia</td>
</tr>
</tbody>
</table>

**Skin and subcutaneous tissue disorders**

| **Uncommon**                   | Rash papular, urticaria, hyperhidrosis, *pruritus* |
| **Rare**                       | *Stevens Johnson syndrome*, cold sweat |

**Musculoskeletal and connective tissue disorders**

| **Common**                     | Muscle cramp, arthralgia, back pain, pain in limb, cervical spasm |
| **Uncommon**                   | Joint swelling, myalgia, muscle twitching, neck pain, muscle stiffness |
| **Rare**                       | Rhabdomyolysis |

**Renal and urinary disorders**

| **Uncommon**                   | Urinary incontinence, dysuria |
| **Rare**                       | Renal failure, oliguria, *urinary retention* |

**Reproductive system and breast disorders**

| **Common**                     | Erectile dysfunction |
| **Uncommon**                   | Sexual dysfunction, ejaculation delayed, dysmenorrhoea, breast pain |
| **Rare**                       | Amenorrhoea, breast discharge, breast enlargement, *gynaecomastia* |

**General disorders and administration site conditions**

| **Common**                     | Oedema peripheral, oedema, gait abnormal, fall, feeling drunk, feeling abnormal, fatigue |
| **Uncommon**                   | Generalised oedema, *face oedema*, chest tightness, pain, pyrexia, thirst, chills, asthenia |

**Investigations**

| **Common**                     | Weight increased |
| **Uncommon**                   | Blood creatine phosphokinase increased, alanine aminotransferase increased, aspartate aminotransferase 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, suggestive of physical dependence. The patient should be informed about this at the start of the treatment.

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

Paediatric population
The pregabalin safety profile observed in two paediatric studies (pharmacokinetic and tolerability study, n=65; 1 year open label follow on safety study, n=54) was similar to that observed in the adult studies (see sections 4.2, 5.1 and 5.2).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

In rare occasions, cases of coma have been reported.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

Mechanism of action
Pregabalin binds to an auxiliary subunit (α2-δ 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 BID or 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.

Paediatric population
The efficacy and safety of pregabalin as adjunctive treatment for epilepsy in paediatric 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 (n=65) were similar to those observed in adults. Results of a 1 year open label safety study in 54 paediatric patients from 3 months to 16 years of age with epilepsy indicate that the adverse events of pyrexia and upper respiratory infections were observed more frequently than in adult studies (see sections 4.2, 4.8 and 5.2).

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

Generalised Anxiety Disorder
Pregabalin has been studied in 6 controlled trials of 4-6 week duration, an elderly study of 8 week duration and a long-term relapse prevention study with a double blind relapse prevention phase of 6 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 C_max by approximately 25-30% and a delay in t_max to approximately 2.5 hours. However, administration of pregabalin with food has no clinically significant effect on the extent of pregabalin absorption.
Distribution
In preclinical studies, pregabalin has been shown to cross the blood brain barrier in mice, rats, and monkeys. Pregabalin has been shown to cross the placenta in rats and is present in the milk of lactating rats. In humans, the apparent volume of distribution of pregabalin following oral administration is approximately 0.56 l/kg. Pregabalin is not bound to plasma proteins.

Biotransformation
Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabelled pregabalin, approximately 98% of the radioactivity recovered in the urine was unchanged pregabalin. The N-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0.9% of the dose. In preclinical studies, there was no indication of racemisation of pregabalin S-enantiomer to the R-enantiomer.

Elimination
Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. Pregabalin mean elimination half-life is 6.3 hours. Pregabalin plasma clearance and renal clearance are directly proportional to creatinine clearance (see section 5.2 Renal impairment).

Dose adjustment in patients with reduced renal function or undergoing haemodialysis is necessary (see section 4.2 Table 1).

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

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

Renal impairment
Pregabalin clearance is directly proportional to creatinine clearance. In addition, pregabalin is effectively removed from plasma by haemodialysis (following a 4 hour haemodialysis treatment plasma pregabalin concentrations are reduced by approximately 50%). Because renal elimination is the major elimination pathway, dose reduction in patients with renal impairment and dose supplementation following haemodialysis is necessary (see section 4.2 Table 1).

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

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

After oral administration of pregabalin in paediatric patients in the fasted state, in general, time to reach peak plasma concentration was similar across the entire age group and occurred 0.5 hours to 2 hours postdose.
Pregabalin $C_{\text{max}}$ and AUC parameters increased in a linear manner with increasing dose within each age group. The AUC was lower by 30% in paediatric patients below a weight of 30 kg due to an increased body weight adjusted clearance of 43% for these patients in comparison to patients weighing ≥30 kg.

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

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

Pregabalin pharmacokinetics in patients younger than 3 months old have not been studied (see sections 4.2, 4.8 and 5.1).

**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 Table 1).

**Breast-feeding mothers**
The pharmacokinetics of 150 mg pregabalin given every 12 hours (300 mg daily dose) was evaluated in 10 lactating women who were at least 12 weeks postpartum. Lactation had little to no influence on pregabalin pharmacokinetics. Pregabalin was excreted into breast milk with average steady-state concentrations approximately 76% of those in maternal plasma. The estimated infant dose from breast milk (assuming mean milk consumption of 150 ml/kg/day) of women receiving 300 mg/day or the maximum dose of 600 mg/day would be 0.31 or 0.62 mg/kg/day, respectively. These estimated doses are approximately 7% of the total daily maternal dose on a mg/kg basis.

### 5.3 Preclinical safety data

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 ≥ 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

Capsule content
Pregelatinised maize starch
Maize starch
Talc

Capsule shell
Gelatin
Titanium dioxide (E171)
Iron oxide yellow (E172)
Iron oxide red (E172)
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.
After first opening of the container: 6 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC/Alu blister.
HDPE container with PP screw cap.

Pack sizes:
Blister packs: 14, 28, 56, 70, 84, 100 or 120 hard capsules
Blister packs (unit dose): 56 x 1, 84 x 1 or 100 x 1 hard capsules.
Container packs: 200 hard capsules

Not all pack sizes may be marketed.
6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Sandoz GmbH
Biochemiestrasse 10
A-6250 Kundl
Austria

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1011/001-010
EU/1/15/1011/084

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 June 2015

10. DATE OF REVISION OF THE TEXT

1. **NAME OF THE MEDICINAL PRODUCT**

Pregabalin Sandoz 50 mg hard capsules

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each hard capsule contains 50 mg of pregabalin.

For the full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Hard capsule.
Light yellow opaque cap and body, capsule size 3 (15.9 mm x 5.8 mm), filled with white to nearly white coloured powder.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

**Neuropathic pain**
Pregabalin Sandoz is indicated for the treatment of peripheral and central neuropathic pain in adults.

**Epilepsy**
Pregabalin Sandoz is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.

**Generalised Anxiety Disorder**
Pregabalin Sandoz 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 individualised according to creatinine clearance (CLcr), as indicated in Table 1 determined using the following formula:

\[
CL_c = \frac{1.23 \times [140 \times \text{age}(\text{years})] \times \text{weight}(\text{kg})}{\text{serum creatinine} \times (\mu\text{mol} / \text{L})} \times 0.85 \text{ for female patients}
\]

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

<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></td>
<td>Starting dose (mg/day)</td>
<td>Maximum dose</td>
</tr>
<tr>
<td>≥ 60</td>
<td>150</td>
<td>600</td>
</tr>
<tr>
<td>≥ 30 - &lt; 60</td>
<td>75</td>
<td>300</td>
</tr>
<tr>
<td>≥ 15 - &lt; 30</td>
<td>25 – 50</td>
<td>150</td>
</tr>
<tr>
<td>&lt; 15</td>
<td>25</td>
<td>75</td>
</tr>
</tbody>
</table>

Supplementary dosage following haemodialysis (mg)

|                               | 25 | 100 | Single dose + |

TID = Three divided doses
BID = Two divided doses
* Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose
+ Supplementary dose is a single additional dose

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

Paediatric population
The safety and efficacy of pregabalin in children below the age of 12 years and in adolescents (12-17 years of age) have not been established. Currently available data are described in section 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

**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**

Pregabalin Sandoz may be taken with or without food.
Pregabalin Sandoz is for oral use only.

### 4.3 Contraindications

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

### 4.4 Special warnings and precautions for use

**Diabetic patients**

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

**Hypersensitivity reactions**

There have been reports in the postmarketing experience of hypersensitivity reactions, including cases of angioedema. Pregabalin should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper 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 postmarketing reports of loss of consciousness, confusion and mental impairment. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medicinal product.

**Vision-related effects**

In controlled trials, a higher proportion of patients treated with pregabalin reported blurred vision than did patients treated with placebo which resolved in a majority of cases with continued dosing. In the clinical studies 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 postmarketing experience, visual adverse reactions have also been reported, including loss of vision, visual blurring or other changes of visual acuity, many of which were transient. Discontinuation of pregabalin may result in resolution or improvement of these visual symptoms.

**Renal failure**

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

**Withdrawal of concomitant antiepileptic medicinal products**

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

**Withdrawal symptoms**
After discontinuation of short-term and long-term treatment with pregabalin, withdrawal symptoms have been observed in some patients. The following events have been mentioned: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, nervousness, depression, pain, convulsion, hyperhidrosis and dizziness, suggestive of physical dependence. The patient should be informed about this at the start of the treatment.

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

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

**Congestive heart failure**

There have been postmarketing reports of congestive heart failure in some patients receiving pregabalin. These reactions are mostly seen in elderly cardiovascular compromised patients during pregabalin treatment for a neuropathic indication. Pregabalin should be used with caution in these patients. Discontinuation of pregabalin may resolve the reaction.

**Treatment of central 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).

**Misuse, abuse potential or dependence**

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

**Encephalopathy**

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

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 Fertility, 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 childbearing potential.

**Pregnancy**

There are no adequate data from the use of pregabalin in pregnant women.

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

Pregabalin Sandoz 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 Sandoz may have minor or moderate influence on the ability to drive and use machines. Pregabalin Sandoz 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 program involved over 8900 patients 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 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 (≥ 1/10); common (≥ 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

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse drug reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Nasopharyngitis</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Neutropaenia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Rare</td>
<td>Angioedema, allergic reaction</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Appetite increased</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Anorexia, hypoglycaemia</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Common</td>
<td>Euphoric mood, confusion, irritability, disorientation, insomnia, libido decreased</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Hallucination, panic attack, restlessness, agitation, depression, depressed mood, elevated mood, aggression, mood swings, depersonalisation, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy</td>
</tr>
<tr>
<td>Rare</td>
<td>Disinhibition</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Very Common</td>
<td>Dizziness, somnolence, headache</td>
</tr>
<tr>
<td>Common</td>
<td>Ataxia, coordination abnormal, tremor, dysarthria, amnesia, memory impairment, disturbance in attention, paraesthesia, hypoesthesia, sedation, balance disorder, lethargy</td>
</tr>
<tr>
<td>Uncommon</td>
<td>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</td>
</tr>
<tr>
<td>Rare</td>
<td>Convulsions, parosmia, hypokinesia, dysgraphia</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Vision blurred, diplopia</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Peripheral vision loss, visual disturbance, eye swelling, visual field defect, visual acuity reduced, eye pain, asthenopia, photopsia, dry eye, laceration increased, eye irritation</td>
</tr>
<tr>
<td>Rare</td>
<td>Vision loss, keratitis, oscillopsia, altered visual depth perception, mydriasis, strabismus, visual brightness</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Vertigo</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Hyperacusis</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Tachycardia, atrioventricular block first degree, sinus bradycardia, congestive heart failure</td>
</tr>
<tr>
<td>Rare</td>
<td>QT prolongation, sinus tachycardia, sinus arrhythmia</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Hypotension, hypertension, hot flushes, flushing, peripheral coldness</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness</td>
</tr>
<tr>
<td>Rare</td>
<td>Pulmonary oedema, throat tightness,</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Vomiting, nausea, constipation, diarrhoea, flatulence, abdominal</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td>distension, dry mouth</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Gastrooesophageal reflux disease, salivary hypersecretion, hypoesthesia oral</td>
</tr>
<tr>
<td>Rare</td>
<td>Ascites, pancreatitis, <strong>swollen tongue</strong>, dysphagia</td>
</tr>
</tbody>
</table>

**Skin and subcutaneous tissue disorders**

| Uncommon | Rash papular, urticaria, hyperhidrosis, **pruritus** |
| Rare | **Stevens Johnson syndrome**, cold sweat |

**Musculoskeletal and connective tissue disorders**

| Common | Muscle cramp, arthralgia, back pain, pain in limb, cervical spasm |
| Uncommon | Joint swelling, myalgia, muscle twitching, neck pain, muscle stiffness |
| Rare | Rhabdomyolysis |

**Renal and urinary disorders**

| Uncommon | Urinary incontinence, dysuria |
| Rare | Renal failure, oliguria, **urinary retention** |

**Reproductive system and breast disorders**

| Common | Erectile dysfunction |
| Uncommon | Sexual dysfunction, ejaculation delayed, dysmenorrhoea, breast pain |
| Rare | Amenorrhoea, breast discharge, breast enlargement, **gynaecomastia** |

**General disorders and administration site conditions**

| Common | Oedema peripheral, oedema, gait abnormal, fall, feeling drunk, feeling abnormal, fatigue |
| Uncommon | Generalised oedema, **face oedema**, chest tightness, pain, pyrexia, thirst, chills, asthenia |

**Investigations**

| Common | Weight increased |
| Uncommon | Blood creatine phosphokinase increased, alanine aminotransferase increased, aspartate aminotransferase 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, suggestive of physical dependence. The patient should be informed about this at the start of the treatment.

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

**Paediatric population**
The pregabalin safety profile observed in two paediatric studies (pharmacokinetic and tolerability study, n=65; 1 year open label follow on safety study, n=54) was similar to that observed in the adult studies (see sections 4.2, 5.1 and 5.2).

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

### 4.9 Overdose

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

In rare occasions, cases of coma have been reported.

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

### 5. PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

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

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

**Mechanism of action**
Pregabalin binds to an auxiliary subunit (α2-δ 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 BID or 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.

Paediatric population

The efficacy and safety of pregabalin as adjunctive treatment for epilepsy in paediatric 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 (n=65) were similar to those observed in adults. Results of a 1 year open label safety study in 54 paediatric patients from 3 months to 16 years of age with epilepsy indicate that the adverse events of pyrexia and upper respiratory infections were observed more frequently than in adult studies (see sections 4.2, 4.8 and 5.2).

Monotherapy (newly diagnosed patients)

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

Generalised Anxiety Disorder

Pregabalin has been studied in 6 controlled trials of 4-6 week duration, an elderly study of 8 week duration and a long-term relapse prevention study with a double blind relapse prevention phase of 6 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 Cmax by approximately 25-30% and a delay
in $t_{\text{max}}$ to approximately 2.5 hours. However, administration of pregabalin with food has no clinically significant effect on the extent of pregabalin absorption.

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

**Biotransformation**
Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabelled pregabalin, approximately 98% of the radioactivity recovered in the urine was unchanged pregabalin. The N-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0.9% of the dose. In preclinical studies, there was no indication of racemisation of pregabalin S-enantiomer to the R-enantiomer.

**Elimination**
Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. Pregabalin mean elimination half-life is 6.3 hours. Pregabalin plasma clearance and renal clearance are directly proportional to creatinine clearance (see section 5.2 Renal impairment).

Dose adjustment in patients with reduced renal function or undergoing haemodialysis is necessary (see section 4.2 Table 1).

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

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

**Renal impairment**
Pregabalin clearance is directly proportional to creatinine clearance. In addition, pregabalin is effectively removed from plasma by haemodialysis (following a 4 hour haemodialysis treatment plasma pregabalin concentrations are reduced by approximately 50%). Because renal elimination is the major elimination pathway, dose reduction in patients with renal impairment and dose supplementation following haemodialysis is necessary (see section 4.2 Table 1).

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

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

Pregabalin $C_{\text{max}}$ and AUC parameters increased in a linear manner with increasing dose within each age group. The AUC was lower by 30% in paediatric patients below a weight of 30 kg due to an increased body weight adjusted clearance of 43% for these patients in comparison to patients weighing ≥30 kg.
Pregabalin terminal half-life averaged about 3 to 4 hours in paediatric patients up to 6 years of age, and 4 to 6 hours in those 7 years of age and older.

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

Pregabalin pharmacokinetics in patients younger than 3 months old have not been studied (see sections 4.2, 4.8 and 5.1).

**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 Table 1).

**Breast-feeding mothers**
The pharmacokinetics of 150 mg pregabalin given every 12 hours (300 mg daily dose) was evaluated in 10 lactating women who were at least 12 weeks postpartum. Lactation had little to no influence on pregabalin pharmacokinetics. Pregabalin was excreted into breast milk with average steady-state concentrations approximately 76% of those in maternal plasma. The estimated infant dose from breast milk (assuming mean milk consumption of 150 ml/kg/day) of women receiving 300 mg/day or the maximum dose of 600 mg/day would be 0.31 or 0.62 mg/kg/day, respectively. These estimated doses are approximately 7% of the total daily maternal dose on a mg/kg basis.

### 5.3 Preclinical safety data

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 ≥ 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

Capsule content
Pregelatinised maize starch
Maize starch
Talc

Capsule shell
Gelatín
Titanium dioxide (E171)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.
After first opening of the container: 6 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC//Alu blister.
HDPE container with PP screw cap.

Pack sizes:
Blister packs: 14, 21, 28, 56, 84 or 100 hard capsules
Blister packs (unit dose): 84 x 1 hard capsules
Container packs: 200 hard capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Sandoz GmbH
Biochemiestrasse 10
A-6250 Kundl
Austria

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1011/011-017
EU/1/15/1011/085

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 June 2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.
1. NAME OF THE MEDICINAL PRODUCT

Pregabalin Sandoz 75 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 75 mg of pregabalin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.
Red opaque cap and white opaque body, capsule size 4 (14.3 mm x 5.3 mm), filled with white to nearly white coloured powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Epilepsy
Pregabalin Sandoz is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.

Generalised Anxiety Disorder
Pregabalin Sandoz 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 individualised according to creatinine clearance (CLcr), as indicated in Table 1 determined using the following formula:

\[
CLr (\text{ml/min}) = \frac{1.23 \times \left[ 140 - \text{age}(\text{years}) \right] \times \text{weight (kg)} \times \text{serum creatinine (\text{\mu mol/L})}}{\text{CLcr} (\text{\text{\text{mg/dL}}})} \times 0.85 \text{ for female patients}
\]

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**

<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></td>
<td>Starting dose (mg/day)</td>
<td>Maximum dose (mg/day)</td>
</tr>
<tr>
<td>≥ 60</td>
<td>150</td>
<td>600</td>
</tr>
<tr>
<td>≥ 30 - &lt; 60</td>
<td>75</td>
<td>300</td>
</tr>
<tr>
<td>≥ 15 - &lt; 30</td>
<td>25 – 50</td>
<td>150</td>
</tr>
<tr>
<td>&lt; 15</td>
<td>25</td>
<td>75</td>
</tr>
</tbody>
</table>

**Supplementary dosage following haemodialysis (mg)**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Supplementary dose following haemodialysis</td>
<td>25</td>
<td>100</td>
</tr>
</tbody>
</table>

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 (see section 5.2).

**Paediatric population**
The safety and efficacy of pregabalin in children below the age of 12 years and in adolescents (12-17 years of age) have not been established. Currently available data are described in section 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

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
Pregabalin Sandoz may be taken with or without food.
Pregabalin Sandoz is for oral use only.

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

4.4 Special warnings and precautions for use

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

Hypersensitivity reactions
There have been reports in the postmarketing experience of hypersensitivity reactions, including cases of angioedema. Pregabalin should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper 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 postmarketing reports of loss of consciousness, confusion and mental impairment. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medicinal product.

Vision-related effects
In controlled trials, a higher proportion of patients treated with pregabalin reported blurred vision than did patients treated with placebo which resolved in a majority of cases with continued dosing. In the clinical studies 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 postmarketing experience, visual adverse reactions have also been reported, including loss of vision, visual blurring or other changes of visual acuity, many of which were transient. Discontinuation of pregabalin may result in resolution or improvement of these visual symptoms.

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

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

Withdrawal symptoms
After discontinuation of short-term and long-term treatment with pregabalin, withdrawal symptoms have been observed in some patients. The following events have been mentioned: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, nervousness, depression, pain, convulsion, hyperhidrosis and dizziness, suggestive of physical dependence. The patient should be informed about this at the start of the treatment.

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

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

**Congestive heart failure**
There have been postmarketing reports of congestive heart failure in some patients receiving pregabalin. These reactions are mostly seen in elderly cardiovascular compromised patients during pregabalin treatment for a neuropathic indication. Pregabalin should be used with caution in these patients. Discontinuation of pregabalin may resolve the reaction.

**Treatment of central 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).

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

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

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 controlled clinical trials, multiple oral doses of pregabalin co-administered with oxycodone, lorazepam, or ethanol did not result in clinically important effects on respiration. In the postmarketing experience, there are reports of respiratory failure and coma in patients taking pregabalin and other central nervous system (CNS) depressant medicinal products. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone.

**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 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 (see section 5.3). The potential risk for humans is unknown.

Pregabalin Sandoz 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 Sandoz may have minor or moderate influence on the ability to drive and use machines. Pregabalin Sandoz 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 program involved over 8900 patients 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 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 (≥ 1/10); common (≥ 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

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse drug reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Nasopharyngitis</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Neutropaenia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Rare</td>
<td>Angioedema, allergic reaction</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Appetite increased</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Anorexia, hypoglycaemia</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>--------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Common</strong></td>
<td>Euphoric mood, confusion, irritability, disorientation, insomnia, libido decreased</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Hallucination, panic attack, restlessness, agitation, depression, depressed mood, elevated mood, aggression, mood swings, depersonalisation, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Disinhibition</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Very Common</strong></td>
<td>Dizziness, somnolence, headache</td>
</tr>
<tr>
<td><strong>Common</strong></td>
<td>Ataxia, coordination abnormal, tremor, dysarthria, amnesia, memory impairment, disturbance in attention, paraesthesia, hypanesthesia, sedation, balance disorder, lethargy</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>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</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Convulsions, parosmia, hypokinesia, dysgraphia</td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Common</strong></td>
<td>Vision blurred, diplopia</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Peripheral vision loss, visual disturbance, eye swelling, visual field defect, visual acuity reduced, eye pain, asthenopia, photopsia, dry eye, laceration increased, eye irritation</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Vision loss, keratitis, oscillopsia, altered visual depth perception, mydriasis, strabismus, visual brightness</td>
</tr>
<tr>
<td><strong>Ear and labyrinth disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Common</strong></td>
<td>Vertigo</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Hyperacusis</td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Tachycardia, atrioventricular block first degree, sinus bradycardia, congestive heart failure</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>QT prolongation, sinus tachycardia, sinus arrhythmia</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Hypotension, hypertension, hot flushes, flushing, peripheral coldness</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Pulmonary oedema, throat tightness,</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Common</strong></td>
<td>Vomiting, nausea, constipation, diarrhoea, flatulence, abdominal</td>
</tr>
<tr>
<td>Common/Treatment</td>
<td>Distension, dry mouth</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Gastrooesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Ascites, pancreatitis, <em>swollen tongue</em>, dysphagia</td>
</tr>
</tbody>
</table>

**Skin and subcutaneous tissue disorders**

<table>
<thead>
<tr>
<th>Common/Treatment</th>
<th>Rash papular, urticaria, hyperhidrosis, <em>pruritus</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rare</strong></td>
<td><em>Stevens Johnson syndrome</em>, cold sweat</td>
</tr>
</tbody>
</table>

**Musculoskeletal and connective tissue disorders**

<table>
<thead>
<tr>
<th>Common/Treatment</th>
<th>Muscle cramp, arthralgia, back pain, pain in limb, cervical spasm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
<td>Joint swelling, myalgia, muscle twitching, neck pain, muscle stiffness</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Rhabdomyolysis</td>
</tr>
</tbody>
</table>

**Renal and urinary disorders**

<table>
<thead>
<tr>
<th>Common/Treatment</th>
<th>Urinary incontinence, dysuria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
<td>Renal failure, oliguria, <em>urinary retention</em></td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Rhabdomyolysis</td>
</tr>
</tbody>
</table>

**Reproductive system and breast disorders**

<table>
<thead>
<tr>
<th>Common/Treatment</th>
<th>Erectile dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
<td>Sexual dysfunction, ejaculation delayed, dysmenorrhoea, breast pain</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Amenorrhoea, breast discharge, breast enlargement, <em>gynaecomastia</em></td>
</tr>
</tbody>
</table>

**General disorders and administration site conditions**

<table>
<thead>
<tr>
<th>Common/Treatment</th>
<th>Oedema peripheral, oedema, gait abnormal, fall, feeling drunk, feeling abnormal, fatigue</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
<td>Generalised oedema, <em>face oedema</em>, chest tightness, pain, pyrexia, thirst, chills, asthenia</td>
</tr>
</tbody>
</table>

**Investigations**

<table>
<thead>
<tr>
<th>Common/Treatment</th>
<th>Weight increased</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
<td>Blood creatine phosphokinase increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood glucose increased, platelet count decreased, blood creatinine increased, blood potassium decreased, weight decreased</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>White blood cell count decreased</td>
</tr>
</tbody>
</table>

**After discontinuation of short-term and long-term treatment with pregabalin withdrawal symptoms have been observed in some patients. The following reactions have been mentioned: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, convulsions, nervousness, depression, pain, hyperhidrosis and dizziness, suggestive of physical dependence. The patient should be informed about this at the start of the treatment.**

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

**Paediatric population**
The pregabalin safety profile observed in two paediatric studies (pharmacokinetic and tolerability study, n=65; 1 year open label follow on safety study, n=54) was similar to that observed in the adult studies (see sections 4.2, 5.1 and 5.2).

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

**4.9 Overdose**

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

In rare occasions, cases of coma have been reported.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

**Mechanism of action**

Pregabalin binds to an auxiliary subunit (α2-δ 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 BID or 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.

**Paediatric population**

The efficacy and safety of pregabalin as adjunctive treatment for epilepsy in paediatric 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 (n=65) were similar to those observed in adults. Results of a 1 year open label safety study in 54 paediatric patients from 3 months to 16 years of age with epilepsy indicate that the adverse events of pyrexia and upper respiratory infections were observed more frequently than in adult studies (see sections 4.2, 4.8 and 5.2).

Monotherapy (newly diagnosed patients)

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

**Generalised Anxiety Disorder**

Pregabalin has been studied in 6 controlled trials of 4-6 week duration, an elderly study of 8 week duration and a long-term relapse prevention study with a double blind relapse prevention phase of 6 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 $C_{\text{max}}$ by approximately 25-30% and a delay in $t_{\text{max}}$ to approximately 2.5 hours. However, administration of pregabalin with food has no clinically significant effect on the extent of pregabalin absorption.
Distribution
In preclinical studies, pregabalin has been shown to cross the blood brain barrier in mice, rats, and monkeys. Pregabalin has been shown to cross the placenta in rats and is present in the milk of lactating rats. In humans, the apparent volume of distribution of pregabalin following oral administration is approximately 0.56 l/kg. Pregabalin is not bound to plasma proteins.

Biotransformation
Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabelled pregabalin, approximately 98% of the radioactivity recovered in the urine was unchanged pregabalin. The N-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0.9% of the dose. In preclinical studies, there was no indication of racemisation of pregabalin S-enantiomer to the R-enantiomer.

Elimination
Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. Pregabalin mean elimination half-life is 6.3 hours. Pregabalin plasma clearance and renal clearance are directly proportional to creatinine clearance (see section 5.2 Renal impairment).

Dose adjustment in patients with reduced renal function or undergoing haemodialysis is necessary (see section 4.2 Table 1).

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

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

Renal impairment
Pregabalin clearance is directly proportional to creatinine clearance. In addition, pregabalin is effectively removed from plasma by haemodialysis (following a 4 hour haemodialysis treatment plasma pregabalin concentrations are reduced by approximately 50%). Because renal elimination is the major elimination pathway, dose reduction in patients with renal impairment and dose supplementation following haemodialysis is necessary (see section 4.2 Table 1).

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

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

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

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

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

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

Pregabalin pharmacokinetics in patients younger than 3 months old have not been studied (see sections 4.2, 4.8 and 5.1).

**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 Table 1).

**Breast-feeding mothers**

The pharmacokinetics of 150 mg pregabalin given every 12 hours (300 mg daily dose) was evaluated in 10 lactating women who were at least 12 weeks postpartum. Lactation had little to no influence on pregabalin pharmacokinetics. Pregabalin was excreted into breast milk with average steady-state concentrations approximately 76% of those in maternal plasma. The estimated infant dose from breast milk (assuming mean milk consumption of 150 ml/kg/day)of women receiving 300 mg/day or the maximum dose of 600 mg/day would be 0.31 or 0.62 mg/kg/day, respectively. These estimated doses are approximately 7% of the total daily maternal dose on a mg/kg basis.

### 5.3 Preclinical safety data

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 ≥ 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
includes 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

Capsule content
Pregelatinised maize starch
Maize starch
Talc

Capsule shell
Gelatin
Titanium dioxide (E171)
Iron oxide yellow (E172)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.
After first opening of the container: 6 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC//Alu blister.
HDPE container with PP screw cap.

Pack sizes:
Blister packs: 14, 21, 28, 56, 70, 84, 100 or 120 hard capsules
Blister packs (unit dose): 14 x 1, 56 x 1, 84 x 1, 100 x 1 or 210 x 1 (3 x 70) hard capsules.
Container packs: 100, 200 or 250 hard capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.
7. MARKETING AUTHORISATION HOLDER

Sandoz GmbH
Biochemiestrasse 10
A-6250 Kundl
Austria

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1011/018-033

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 June 2015

10. DATE OF REVISION OF THE TEXT

1. **NAME OF THE MEDICINAL PRODUCT**

Pregabalin Sandoz 100 mg hard capsules

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each hard capsule contains 100 mg of pregabalin.

For the full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Hard capsule.
Red opaque cap and body, capsule size 3 (15.9 mm x 5.8 mm), filled with white to nearly white coloured powder.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

**Neuropathic pain**
Pregabalin Sandoz is indicated for the treatment of peripheral and central neuropathic pain in adults.

**Epilepsy**
Pregabalin Sandoz is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.

**Generalised Anxiety Disorder**
Pregabalin Sandoz 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 individualised according to creatinine clearance (CLcr), as indicated in Table 1 determined using the following formula:

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

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**

<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></td>
<td>Starting dose (mg/day)</td>
<td>Maximum dose (mg/day)</td>
</tr>
<tr>
<td>≥ 60</td>
<td>150</td>
<td>600</td>
</tr>
<tr>
<td>≥ 30 - &lt; 60</td>
<td>75</td>
<td>300</td>
</tr>
<tr>
<td>≥ 15 - &lt; 30</td>
<td>25 – 50</td>
<td>150</td>
</tr>
<tr>
<td>&lt; 15</td>
<td>25</td>
<td>75</td>
</tr>
<tr>
<td>Supplementary dosage following haemodialysis (mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>100</td>
</tr>
</tbody>
</table>

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 (see section 5.2).

**Paediatric population**
The safety and efficacy of pregabalin in children below the age of 12 years and in adolescents (12-17 years of age) have not been established. Currently available data are described in section 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

_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**
Pregabalin Sandoz may be taken with or without food.
Pregabalin Sandoz is for oral use only.

### 4.3 Contraindications

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

### 4.4 Special warnings and precautions for use

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

**Hypersensitivity reactions**
There have been reports in the postmarketing experience of hypersensitivity reactions, including cases of angioedema. Pregabalin should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper 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 postmarketing reports of loss of consciousness, confusion and mental impairment. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medicinal product.

**Vision-related effects**
In controlled trials, a higher proportion of patients treated with pregabalin reported blurred vision than did patients treated with placebo which resolved in a majority of cases with continued dosing. In the clinical studies 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 postmarketing experience, visual adverse reactions have also been reported, including loss of vision, visual blurring or other changes of visual acuity, many of which were transient. Discontinuation of pregabalin may result in resolution or improvement of these visual symptoms.

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

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

**Withdrawal symptoms**
After discontinuation of short-term and long-term treatment with pregabalin, withdrawal symptoms have been observed in some patients. The following events have been mentioned: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, nervousness, depression, pain, convulsion, hyperhidrosis and dizziness, suggestive of physical dependence. The patient should be informed about this at the start of the treatment.

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

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

**Congestive heart failure**
There have been postmarketing reports of congestive heart failure in some patients receiving pregabalin. These reactions are mostly seen in elderly cardiovascular compromised patients during pregabalin treatment for a neuropathic indication. Pregabalin should be used with caution in these patients. Discontinuation of pregabalin may resolve the reaction.

**Treatment of central 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 postmarketing reports of events related to reduced lower gastrointestinal tract function (e.g. intestinal obstruction, paralytic ileus, constipation) when pregabalin was co-administered with medications that have the potential to produce constipation, such as opioid analgesics. When pregabalin and opioids will be used in combination, measures to prevent constipation may be considered (especially in female patients and elderly).

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

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

**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 controlled clinical trials, multiple oral doses of pregabalin co-administered with oxycodone, lorazepam, or ethanol did not result in clinically important effects on respiration. In the postmarketing experience, there are reports of respiratory failure and coma in patients taking pregabalin and other central nervous system (CNS) depressant medicinal products. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone.

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 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 (see section 5.3). The potential risk for humans is unknown.

Pregabalin Sandoz 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 Sandoz may have minor or moderate influence on the ability to drive and use machines. Pregabalin Sandoz 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 program involved over 8900 patients 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 (≥ 1/10); common (≥ 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

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse drug reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Nasopharyngitis</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Neutropaenia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Rare</td>
<td>Angioedema, allergic reaction</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Appetite increased</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Anorexia, hypoglycaemia</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
</tr>
<tr>
<td>------------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td><strong>Common</strong></td>
<td>Euphoric mood, confusion, irritability, disorientation, insomnia, libido decreased</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Hallucination, panic attack, restlessness, agitation, depression, depressed mood, elevated mood, aggression, mood swings, depersonalisation, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Disinhibition</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very Common</strong></td>
<td>Dizziness, somnolence, headache</td>
</tr>
<tr>
<td><strong>Common</strong></td>
<td>Ataxia, coordination abnormal, tremor, dysarthria, amnesia, memory impairment, disturbance in attention, paraesthesia, hypoesthesia, sedation, balance disorder, lethargy</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>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</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Convulsions, parosmia, hypokinesia, dysgraphia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Eye disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
<td>Vision blurred, diplopia</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Peripheral vision loss, visual disturbance, eye swelling, visual field defect, visual acuity reduced, eye pain, asthenopia, photopsia, dry eye, lacrimation increased, eye irritation</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Vision loss, keratitis, oscillopsia, altered visual depth perception, mydriasis, strabismus, visual brightness</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ear and labyrinth disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
<td>Vertigo</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Hyperacusis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiac disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
<td>Tachycardia, atrioventricular block first degree, sinus bradycardia, congestive heart failure</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>QT prolongation, sinus tachycardia, sinus arrhythmia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
<td>Hypotension, hypertension, hot flushes, flushing, peripheral coldness</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiratory, thoracic and mediastinal disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
<td>Dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Pulmonary oedema, throat tightness,</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
<td>Vomiting, nausea, constipation, diarrhoea, flatulence, abdominal</td>
</tr>
<tr>
<td><strong>Distension, dry mouth</strong></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Gastrooesophageal reflux disease, salivary hypersecretion, hypoesthesia oral</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Ascites, pancreatitis, swollen tongue, dysphagia</td>
</tr>
</tbody>
</table>

**Skin and subcutaneous tissue disorders**

<table>
<thead>
<tr>
<th><strong>Skin and subcutaneous tissue disorders</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
<td>Rash papular, urticaria, hyperhidrosis, pruritus</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Stevens Johnson syndrome, cold sweat</td>
</tr>
</tbody>
</table>

**Musculoskeletal and connective tissue disorders**

<table>
<thead>
<tr>
<th><strong>Musculoskeletal and connective tissue disorders</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
<td>Muscle cramp, arthralgia, back pain, pain in limb, cervical spasm</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Joint swelling, myalgia, muscle twitching, neck pain, muscle stiffness</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Rhabdomyolysis</td>
</tr>
</tbody>
</table>

**Renal and urinary disorders**

<table>
<thead>
<tr>
<th><strong>Renal and urinary disorders</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
<td>Urinary incontinence, dysuria</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Renal failure, oliguria, urinary retention</td>
</tr>
</tbody>
</table>

**Reproductive system and breast disorders**

<table>
<thead>
<tr>
<th><strong>Reproductive system and breast disorders</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
<td>Erectile dysfunction</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Sexual dysfunction, ejaculation delayed, dysmenorrhoea, breast pain</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Amenorrhoea, breast discharge, breast enlargement, gynaecomastia</td>
</tr>
</tbody>
</table>

**General disorders and administration site conditions**

<table>
<thead>
<tr>
<th><strong>General disorders and administration site conditions</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
<td>Oedema peripheral, oedema, gait abnormal, fall, feeling drunk, feeling abnormal, fatigue</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Generalised oedema, face oedema, chest tightness, pain, pyrexia, thirst, chills, asthenia</td>
</tr>
</tbody>
</table>

**Investigations**

<table>
<thead>
<tr>
<th><strong>Investigations</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
<td>Weight increased</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Blood creatine phosphokinase increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood glucose increased, platelet count decreased, blood creatinine increased, blood potassium decreased, weight decreased</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>White blood cell count decreased</td>
</tr>
</tbody>
</table>

After discontinuation of short-term and long-term treatment with pregabalin withdrawal symptoms have been observed in some patients. The following reactions have been mentioned: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, convulsions, nervousness, depression, pain, hyperhidrosis and dizziness, suggestive of physical dependence. The patient should be informed about this at the start of the treatment.

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

*Paediatric population*
The pregabalin safety profile observed in two paediatric studies (pharmacokinetic and tolerability study, n=65; 1 year open label follow on safety study, n=54) was similar to that observed in the adult studies (see sections 4.2, 5.1 and 5.2).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

In rare occasions, cases of coma have been reported.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

Mechanism of action
Pregabalin binds to an auxiliary subunit (α2-δ 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 BID or 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.

Paediatric population

The efficacy and safety of pregabalin as adjunctive treatment for epilepsy in paediatric 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 (n=65) were similar to those observed in adults. Results of a 1 year open label safety study in 54 paediatric patients from 3 months to 16 years of age with epilepsy indicate that the adverse events of pyrexia and upper respiratory infections were observed more frequently than in adult studies (see sections 4.2, 4.8 and 5.2).

Monotherapy (newly diagnosed patients)

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

Generalised Anxiety Disorder

Pregabalin has been studied in 6 controlled trials of 4-6 week duration, an elderly study of 8 week duration and a long-term relapse prevention study with a double blind relapse prevention phase of 6 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 $C_{\text{max}}$ by approximately 25-30% and a delay
in $t_{\text{max}}$, to approximately 2.5 hours. However, administration of pregabalin with food has no clinically significant effect on the extent of pregabalin absorption.

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

**Biotransformation**
Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabelled pregabalin, approximately 98% of the radioactivity recovered in the urine was unchanged pregabalin. The N-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0.9% of the dose. In preclinical studies, there was no indication of racemisation of pregabalin S-enantiomer to the R-enantiomer.

**Elimination**
Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. Pregabalin mean elimination half-life is 6.3 hours. Pregabalin plasma clearance and renal clearance are directly proportional to creatinine clearance (see section 5.2 Renal impairment). Dose adjustment in patients with reduced renal function or undergoing haemodialysis is necessary (see section 4.2 Table 1).

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

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

**Renal impairment**
Pregabalin clearance is directly proportional to creatinine clearance. In addition, pregabalin is effectively removed from plasma by haemodialysis (following a 4 hour haemodialysis treatment plasma pregabalin concentrations are reduced by approximately 50%). Because renal elimination is the major elimination pathway, dose reduction in patients with renal impairment and dose supplementation following haemodialysis is necessary (see section 4.2 Table 1).

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

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

After oral administration of pregabalin in paediatric patients in the fasted state, in general, time to reach peak plasma concentration was similar across the entire age group and occurred 0.5 hours to 2 hours postdose.
Pregabalin \( \text{C}_{\text{max}} \) and AUC parameters increased in a linear manner with increasing dose within each age group. The AUC was lower by 30% in paediatric patients below a weight of 30 kg due to an increased body weight adjusted clearance of 43% for these patients in comparison to patients weighing \( \geq 30 \text{ kg} \).

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

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

Pregabalin pharmacokinetics in patients younger than 3 months old have not been studied (see sections 4.2, 4.8 and 5.1).

Elderly (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 Table 1).

Breast-feeding mothers
The pharmacokinetics of 150 mg pregabalin given every 12 hours (300 mg daily dose) was evaluated in 10 lactating women who were at least 12 weeks postpartum. Lactation had little to no influence on pregabalin pharmacokinetics. Pregabalin was excreted into breast milk with average steady-state concentrations approximately 76% of those in maternal plasma. The estimated infant dose from breast milk (assuming mean milk consumption of 150 ml/kg/day of women receiving 300 mg/day or the maximum dose of 600 mg/day would be 0.31 or 0.62 mg/kg/day, respectively. These estimated doses are approximately 7% of the total daily maternal dose on a mg/kg basis.

5.3 Preclinical safety data

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 \( \geq 2 \) 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 \textit{in vitro} and \textit{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 oestrous 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

Capsule content
Pregelatinised maize starch
Maize starch
Talc

Capsule shell
Gelatin
Titanium dioxide (E171)
Iron oxide yellow (E172)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC//Alu blister.

Pack sizes:
Blister packs: 14, 21, 28, 56, 84 or 100 hard capsules
Blister packs (unit dose): 84 x 1 or 100 x 1 hard capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER
8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1011/034-041

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 June 2015

10. DATE OF REVISION OF THE TEXT

1. **NAME OF THE MEDICINAL PRODUCT**

Pregabalin Sandoz 150 mg hard capsules

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each hard capsule contains 150 mg of pregabalin.

For the full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Hard capsule.
White opaque cap and body, capsule size 2 (18.0 mm x 6.4 mm), filled with white to nearly white coloured powder.

4. **CLINICAL PARTICULARS**

4.1 Therapeutic indications

**Neuropathic pain**
Pregabalin Sandoz is indicated for the treatment of peripheral and central neuropathic pain in adults.

**Epilepsy**
Pregabalin Sandoz is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.

**Generalised Anxiety Disorder**
Pregabalin Sandoz 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 individualised according to creatinine clearance (CLcr), as indicated in Table 1 determined using the following formula:

\[
CLr (\text{ml/min}) = \frac{1.23 \times [140 - \text{age (years)}] \times \text{weight (kg)}}{\text{serum creatinine (\text{\textmu}mol/l)}} \times 0.85 \text{ for female patients}
\]

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

<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></td>
<td>Starting dose (mg/day)</td>
<td>Maximum dose (mg/day)</td>
</tr>
<tr>
<td>≥ 60</td>
<td>150</td>
<td>600</td>
</tr>
<tr>
<td>≥ 30 - &lt; 60</td>
<td>75</td>
<td>300</td>
</tr>
<tr>
<td>≥ 15 - &lt; 30</td>
<td>25 – 50</td>
<td>150</td>
</tr>
<tr>
<td>&lt; 15</td>
<td>25</td>
<td>75</td>
</tr>
<tr>
<td>Supplementary dosage following haemodialysis (mg)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

|                              | 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 (see section 5.2).

Paediatric population
The safety and efficacy of pregabalin in children below the age of 12 years and in adolescents (12-17 years of age) have not been established. Currently available data are described in section 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

**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**
Pregabalin Sandoz may be taken with or without food.
Pregabalin Sandoz is for oral use only.

### 4.3 Contraindications

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

### 4.4 Special warnings and precautions for use

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

**Hypersensitivity reactions**
There have been reports in the postmarketing experience of hypersensitivity reactions, including cases of angioedema. Pregabalin should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper 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 postmarketing reports of loss of consciousness, confusion and mental impairment. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medicinal product.

**Vision-related effects**
In controlled trials, a higher proportion of patients treated with pregabalin reported blurred vision than did patients treated with placebo which resolved in a majority of cases with continued dosing. In the clinical studies 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 postmarketing experience, visual adverse reactions have also been reported, including loss of vision, visual blurring or other changes of visual acuity, many of which were transient. Discontinuation of pregabalin may result in resolution or improvement of these visual symptoms.

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

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

**Withdrawal symptoms**
After discontinuation of short-term and long-term treatment with pregabalin, withdrawal symptoms have been observed in some patients. The following events have been mentioned: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, nervousness, depression, pain, convulsion, hyperhidrosis and dizziness, suggestive of physical dependence. The patient should be informed about this at the start of the treatment.

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

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

**Congestive heart failure**
There have been postmarketing reports of congestive heart failure in some patients receiving pregabalin. These reactions are mostly seen in elderly cardiovascular compromised patients during pregabalin treatment for a neuropathic indication. Pregabalin should be used with caution in these patients. Discontinuation of pregabalin may resolve the reaction.

**Treatment of central 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 postmarketing reports of events related to reduced lower gastrointestinal tract function (e.g., intestinal obstruction, paralytic ileus, constipation) when pregabalin was co-administered with medications that have the potential to produce constipation, such as opioid analgesics. When pregabalin and opioids will be used in combination, measures to prevent constipation may be considered (especially in female patients and elderly).

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

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

**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 controlled clinical trials, multiple oral doses of pregabalin co-administered with oxycodone, lorazepam, or ethanol did not result in clinically important effects on respiration. In the postmarketing experience, there are reports of respiratory failure and coma in patients taking pregabalin and other central nervous system (CNS) depressant medicinal products. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone.

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 in males and females
As the potential risk for humans is unknown, effective contraception must be used in women of childbearing potential.

Pregnancy
There are no adequate data from the use of pregabalin in pregnant women.

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

Pregabalin Sandoz 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 Sandoz may have minor or moderate influence on the ability to drive and use machines. Pregabalin Sandoz 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 program involved over 8900 patients 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 (≥ 1/10); common (≥ 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

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse drug reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Nasopharyngitis</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Neutropaenia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Rare</td>
<td>Angioedema, allergic reaction</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Appetite increased</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Anorexia, hypoglycaemia</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Common</td>
<td>Euphoric mood, confusion, irritability, disorientation, insomnia, libido decreased</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Hallucination, panic attack, restlessness, agitation, depression, depressed mood, elevated mood, aggression, mood swings, depersonalisation, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy</td>
</tr>
<tr>
<td>Rare</td>
<td>Disinhibition</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Nervous system disorders</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Common</td>
<td>Dizziness, somnolence, headache</td>
</tr>
<tr>
<td>Common</td>
<td>Ataxia, coordination abnormal, tremor, dysarthria, amnesia, memory impairment, disturbance in attention, paraesthesia, hyypoesthesia, sedation, balance disorder, lethargy</td>
</tr>
<tr>
<td>Uncommon</td>
<td>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</td>
</tr>
<tr>
<td>Rare</td>
<td>Convulsions, parosmia, hypokinesia, dysgraphia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Eye disorders</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Vision blurred, diplopia</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Peripheral vision loss, visual disturbance, eye swelling, visual field defect, visual acuity reduced, eye pain, asthenopia, photopsia, dry eye, lacrimation increased, eye irritation</td>
</tr>
<tr>
<td>Rare</td>
<td>Vision loss, keratitis, oscillopsia, altered visual depth perception, mydriasis, strabismus, visual brightness</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Ear and labyrinth disorders</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Vertigo</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Hyperacusis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Cardiac disorders</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Tachycardia, atrioventricular block first degree, sinus bradycardia, congestive heart failure</td>
</tr>
<tr>
<td>Rare</td>
<td>QT prolongation, sinus tachycardia, sinus arrhythmia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Vascular disorders</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Hypotension, hypertension, hot flushes, flushing, peripheral coldness</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Respiratory, thoracic and mediastinal disorders</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness</td>
</tr>
<tr>
<td>Rare</td>
<td>Pulmonary oedema, throat tightness,</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Gastrointestinal disorders</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Vomiting, nausea, constipation, diarrhoea, flatulence, abdominal</td>
</tr>
</tbody>
</table>

64
<table>
<thead>
<tr>
<th>Disorders</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Distension, dry mouth</strong></td>
<td>Uncommon Gastrooesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td>Rare Ascites, pancreatitis, <strong>swollen tongue</strong>, dysphagia</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td>Uncommon Rash papular, urticaria, hyperhidrosis, <strong>pruritus</strong></td>
</tr>
</tbody>
</table>
| **Rare**  
**Stevens Johnson syndrome, cold sweat**                           | **Musculoskeletal and connective tissue disorders**                                          |
| **Common** Muscle cramp, arthralgia, back pain, pain in limb, cervical spasm | **Musculoskeletal and connective tissue disorders**                                          |
| **Uncommon**  
**Joint swelling, myalgia, muscle twitching, neck pain, muscle stiffness** | **Musculoskeletal and connective tissue disorders**                                          |
| **Rare**  
**Rhabdomyolysis**                                                   | **Renal and urinary disorders**                                                              |
| **Uncommon** Urinary incontinence, dysuria                              | **Renal and urinary disorders**                                                              |
| **Rare**  
**Renal failure, oliguria, urinary retention**                        | **Renal and urinary disorders**                                                              |
| **Reproductive system and breast disorders**                            | Common Erectile dysfunction  
**Reproductive system and breast disorders**                                                   |
| **Uncommon**  
**Sexual dysfunction, ejaculation delayed, dysmenorrhoea, breast pain** | **Reproductive system and breast disorders**                                                 |
| **Rare**  
**Amenorrhoea, breast discharge, breast enlargement, gynaecomastia** | **Reproductive system and breast disorders**                                                 |
| **General disorders and administration site conditions**                | **General disorders and administration site conditions**                                   |
| **Common** Oedema peripheral, oedema, gait abnormal, fall, feeling drunk, feeling abnormal, fatigue | **General disorders and administration site conditions**                                   |
| **Uncommon** Generalised oedema, **face oedema**, chest tightness, pain, pyrexia, thirst, chills, asthenia | **General disorders and administration site conditions**                                   |
| **Investigations**                                                      | **Investigations**                                                                          |
| **Common** Weight increased                                             | **Investigations**                                                                          |
| **Uncommon** Blood creatine phosphokinase increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood glucose increased, platelet count decreased, blood creatinine increased, blood potassium decreased, weight decreased | **Investigations**                                                                          |
| **Rare**  
**White blood cell count decreased**                               | **Investigations**                                                                          |

After discontinuation of short-term and long-term treatment with pregabalin withdrawal symptoms have been observed in some patients. The following reactions have been mentioned: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, convulsions, nervousness, depression, pain, hyperhidrosis and dizziness, suggestive of physical dependence. The patient should be informed about this at the start of the treatment.

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

**Paediatric population**
The pregabalin safety profile observed in two paediatric studies (pharmacokinetic and tolerability study, n=65; 1 year open label follow on safety study, n=54) was similar to that observed in the adult studies (see sections 4.2, 5.1 and 5.2).

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

**4.9 Overdose**

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

In rare occasions, cases of coma have been reported.

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

**5. PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

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

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

**Mechanism of action**

Pregabalin binds to an auxiliary subunit (α2-δ 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 BID or 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.

**Paediatric population**
The efficacy and safety of pregabalin as adjunctive treatment for epilepsy in paediatric 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 (n=65) were similar to those observed in adults. Results of a 1 year open label safety study in 54 paediatric patients from 3 months to 16 years of age with epilepsy indicate that the adverse events of pyrexia and upper respiratory infections were observed more frequently than in adult studies (see sections 4.2, 4.8 and 5.2).

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

**Generalised Anxiety Disorder**
Pregabalin has been studied in 6 controlled trials of 4-6 week duration, an elderly study of 8 week duration and a long-term relapse prevention study with a double blind relapse prevention phase of 6 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 $C_{max}$ by approximately 25-30% and a delay in $t_{max}$ to
approximately 2.5 hours. However, administration of pregabalin with food has no clinically significant effect on the extent of pregabalin absorption.

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

**Biotransformation**
Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabelled pregabalin, approximately 98% of the radioactivity recovered in the urine was unchanged pregabalin. The N-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0.9% of the dose. In preclinical studies, there was no indication of racemisation of pregabalin S-enantiomer to the R-enantiomer.

**Elimination**
Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. Pregabalin mean elimination half-life is 6.3 hours. Pregabalin plasma clearance and renal clearance are directly proportional to creatinine clearance (see section 5.2 Renal impairment).

Dose adjustment in patients with reduced renal function or undergoing haemodialysis is necessary (see section 4.2 Table 1).

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

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

**Renal impairment**
Pregabalin clearance is directly proportional to creatinine clearance. In addition, pregabalin is effectively removed from plasma by haemodialysis (following a 4 hour haemodialysis treatment plasma pregabalin concentrations are reduced by approximately 50%). Because renal elimination is the major elimination pathway, dose reduction in patients with renal impairment and dose supplementation following haemodialysis is necessary (see section 4.2 Table 1).

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

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

After oral administration of pregabalin in paediatric patients in the fasted state, in general, time to reach peak plasma concentration was similar across the entire age group and occurred 0.5 hours to 2 hours postdose.
Pregabalin $C_{\text{max}}$ and AUC parameters increased in a linear manner with increasing dose within each age group. The AUC was lower by 30% in paediatric patients below a weight of 30 kg due to an increased body weight adjusted clearance of 43% for these patients in comparison to patients weighing $\geq 30$ kg.

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

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

Pregabalin pharmacokinetics in patients younger than 3 months old have not been studied (see sections 4.2, 4.8 and 5.1).

**Elderly (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 Table 1).

**Breast-feeding mothers**

The pharmacokinetics of 150 mg pregabalin given every 12 hours (300 mg daily dose) was evaluated in 10 lactating women who were at least 12 weeks postpartum. Lactation had little to no influence on pregabalin pharmacokinetics. Pregabalin was excreted into breast milk with average steady-state concentrations approximately 76% of those in maternal plasma. The estimated infant dose from breast milk (assuming mean milk consumption of 150 ml/kg/day) of women receiving 300 mg/day or the maximum dose of 600 mg/day would be 0.31 or 0.62 mg/kg/day, respectively. These estimated doses are approximately 7% of the total daily maternal dose on a mg/kg basis.

5.3 Preclinical safety data

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

Capsule content
Pregelatinised maize starch
Maize starch
Talc

Capsule shell
Gelatin
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.
After first opening of the container: 6 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC//Alu blister.
HDPE container with PP screw cap.

Pack sizes:
Blister packs: 14, 21, 28, 56, 70, 84, 100 or 120 hard capsules
Blister packs (unit dose): 56 x 1, 84 x 1, 100 x 1 or 210 x 1 (3 x 70) hard capsules
Container packs: 100, 200 or 250 hard capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
No special requirements for disposal.

7. MARKETING AUTHORIZATION HOLDER

Sandoz GmbH
Biochemiestrasse 10
A-6250 Kundl
Austria

8. MARKETING AUTHORIZATION NUMBER(S)

EU/1/15/1011/042-056

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorisation: 19 June 2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.
1. NAME OF THE MEDICINAL PRODUCT

Pregabalin Sandoz 200 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 200 mg of pregabalin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.
Pale orange opaque cap and body, capsule size 1 (19.4 mm x 6.9 mm), filled with white to nearly white coloured powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Epilepsy
Pregabalin Sandoz is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.

Generalised Anxiety Disorder
Pregabalin Sandoz 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 individualised according to creatinine clearance (CLcr), as indicated in Table 1 determined using the following formula:

\[
CLr (\text{ml/min}) = \left( \frac{1.23 \times [140 - \text{age (years)}] \times \text{weight (kg)}}{\text{serum creatinine (\text{\(\mu\)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

<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></td>
<td>Starting dose (mg/day)</td>
<td>Maximum dose (mg/day)</td>
</tr>
<tr>
<td>≥ 60</td>
<td>150</td>
<td>600</td>
</tr>
<tr>
<td>≥ 30 - &lt; 60</td>
<td>75</td>
<td>300</td>
</tr>
<tr>
<td>≥ 15 - &lt; 30</td>
<td>25 - 50</td>
<td>150</td>
</tr>
<tr>
<td>&lt; 15</td>
<td>25</td>
<td>75</td>
</tr>
</tbody>
</table>

Supplementary dosage following haemodialysis (mg)

| Supplementary dosage following haemodialysis (mg) | 25 | 100 | Single dose + |

TID = Three divided doses
BID = Two divided doses
* Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose
+ Supplementary dose is a single additional dose

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

**Paediatric population**
The safety and efficacy of pregabalin in children below the age of 12 years and in adolescents (12-17 years of age) have not been established. Currently available data are described in section 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

**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**
Pregabalin Sandoz may be taken with or without food.
Pregabalin Sandoz is for oral use only.

### 4.3 Contraindications

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

### 4.4 Special warnings and precautions for use

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

**Hypersensitivity reactions**
There have been reports in the postmarketing experience of hypersensitivity reactions, including cases of angioedema. Pregabalin should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper 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 postmarketing reports of loss of consciousness, confusion and mental impairment. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medicinal product.

**Vision-related effects**
In controlled trials, a higher proportion of patients treated with pregabalin reported blurred vision than did patients treated with placebo which resolved in a majority of cases with continued dosing. In the clinical studies 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 postmarketing experience, visual adverse reactions have also been reported, including loss of vision, visual blurring or other changes of visual acuity, many of which were transient. Discontinuation of pregabalin may result in resolution or improvement of these visual symptoms.

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

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

**Withdrawal symptoms**
After discontinuation of short-term and long-term treatment with pregabalin, withdrawal symptoms have been observed in some patients. The following events have been mentioned: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, nervousness, depression, pain, convulsion, hyperhidrosis and dizziness, suggestive of physical dependence. The patient should be informed about this at the start of the treatment.

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

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

**Congestive heart failure**
There have been postmarketing reports of congestive heart failure in some patients receiving pregabalin. These reactions are mostly seen in elderly cardiovascular compromised patients during pregabalin treatment for a neuropathic indication. Pregabalin should be used with caution in these patients. Discontinuation of pregabalin may resolve the reaction.

**Treatment of central 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).

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

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

**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 controlled clinical trials, multiple oral doses of pregabalin co-administered with oxycodone, lorazepam, or ethanol did not result in clinically important effects on respiration. In the postmarketing experience, there are reports of respiratory failure and coma in patients taking pregabalin and other central nervous system (CNS) depressant medicinal products. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone.

**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 in males and females**
As the potential risk for humans is unknown, effective contraception must be used in women of childbearing potential.

**Pregnancy**
There are no adequate data from the use of pregabalin in pregnant women.

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

Pregabalin Sandoz 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. 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 Sandoz may have minor or moderate influence on the ability to drive and use machines. Pregabalin Sandoz 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 program involved over 8900 patients 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 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 (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 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

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse drug reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Nasopharyngitis</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Neutropaenia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Rare</td>
<td>Angioedema, allergic reaction</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Appetite increased</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Anorexia, hypoglycaemia</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>---</td>
</tr>
<tr>
<td><strong>Common</strong></td>
<td>Euphoric mood, confusion, irritability, disorientation, insomnia, libido decreased</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Hallucination, panic attack, restlessness, agitation, depression, depressed mood, elevated mood, aggression, mood swings, depersonalisation, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Disinhibition</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very Common</strong></td>
<td>Dizziness, somnolence, headache</td>
</tr>
<tr>
<td><strong>Common</strong></td>
<td>Ataxia, coordination abnormal, tremor, dysarthria, amnesia, memory impairment, disturbance in attention, paraesthesia, hypoaesthesia, sedation, balance disorder, lethargy</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>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</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Convulsions, parosmia, hypokinesia, dysgraphia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Eye disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
<td>Vision blurred, diplopia</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Peripheral vision loss, visual disturbance, eye swelling, visual field defect, visual acuity reduced, eye pain, asthenopia, photopsia, dry eye, lacrimation increased, eye irritation</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Vision loss, keratitis, oscillopsia, altered visual depth perception, mydriasis, strabismus, visual brightness</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ear and labyrinth disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
<td>Vertigo</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Hyperacusis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiac disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
<td>Tachycardia, atrioventricular block first degree, sinus bradycardia, congestive heart failure</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>QT prolongation, sinus tachycardia, sinus arrhythmia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
<td>Hypotension, hypertension, hot flushes, flushing, peripheral coldness</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiratory, thoracic and mediastinal disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
<td>Dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Pulmonary oedema, throat tightness,</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
<td>Vomiting, nausea, constipation, diarrhoea, flatulence, abdominal</td>
</tr>
</tbody>
</table>
distension, dry mouth

Uncommon Gastrooesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral

Rare Ascites, pancreatitis, swollen tongue, dysphagia

Skin and subcutaneous tissue disorders

Uncommon Rash papular, urticaria, hyperhidrosis, pruritus

Rare Stevens Johnson syndrome, cold sweat

Musculoskeletal and connective tissue disorders

Common Muscle cramp, arthralgia, back pain, pain in limb, cervical spasm

Uncommon Joint swelling, myalgia, muscle twitching, neck pain, muscle stiffness

Rare Rhabdomyolysis

Renal and urinary disorders

Uncommon Urinary incontinence, dysuria

Rare Renal failure, oliguria, urinary retention

Reproductive system and breast disorders

Common Erectile dysfunction

Uncommon Sexual dysfunction, ejaculation delayed, dysmenorrhoea, breast pain

Rare Amenorrhoea, breast discharge, breast enlargement, gynaecomastia

General disorders and administration site conditions

Common Oedema peripheral, oedema, gait abnormal, fall, feeling drunk, feeling abnormal, fatigue

Uncommon Generalised oedema, face oedema, chest tightness, pain, pyrexia, thirst, chills, asthenia

Investigations

Common Weight increased

Uncommon Blood creatine phosphokinase increased, alanine aminotransferase increased, aspartate aminotransferase 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, suggestive of physical dependence. The patient should be informed about this at the start of the treatment.

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

Paediatric population
The pregabalin safety profile observed in two paediatric studies (pharmacokinetic and tolerability study, n=65; 1 year open label follow on safety study, n=54) was similar to that observed in the adult studies (see sections 4.2, 5.1 and 5.2).

**Reporting of suspected adverse reactions**
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

In rare occasions, cases of coma have been reported.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

**Mechanism of action**
Pregabalin binds to an auxiliary subunit (α2-δ 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 BID or 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.

Paediatric population

The efficacy and safety of pregabalin as adjunctive treatment for epilepsy in paediatric 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 (n=65) were similar to those observed in adults. Results of a 1 year open label safety study in 54 paediatric patients from 3 months to 16 years of age with epilepsy indicate that the adverse events of pyrexia and upper respiratory infections were observed more frequently than in adult studies (see sections 4.2, 4.8 and 5.2).

Monotherapy (newly diagnosed patients)

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

Generalised Anxiety Disorder

Pregabalin has been studied in 6 controlled trials of 4-6 week duration, an elderly study of 8 week duration and a long-term relapse prevention study with a double blind relapse prevention phase of 6 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 Cmax by approximately 25-30% and a delay
in $t_{\text{max}}$ to approximately 2.5 hours. However, administration of pregabalin with food has no clinically significant effect on the extent of pregabalin absorption.

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

**Biotransformation**
Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabelled pregabalin, approximately 98% of the radioactivity recovered in the urine was unchanged pregabalin. The N-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0.9% of the dose. In preclinical studies, there was no indication of racemisation of pregabalin S-enantiomer to the R-enantiomer.

**Elimination**
Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. Pregabalin mean elimination half-life is 6.3 hours. Pregabalin plasma clearance and renal clearance are directly proportional to creatinine clearance (see section 5.2 Renal impairment).

Dose adjustment in patients with reduced renal function or undergoing haemodialysis is necessary (see section 4.2 Table 1).

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

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

**Renal impairment**
Pregabalin clearance is directly proportional to creatinine clearance. In addition, pregabalin is effectively removed from plasma by haemodialysis (following a 4 hour haemodialysis treatment plasma pregabalin concentrations are reduced by approximately 50%). Because renal elimination is the major elimination pathway, dose reduction in patients with renal impairment and dose supplementation following haemodialysis is necessary (see section 4.2 Table 1).

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

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

After oral administration of pregabalin in paediatric patients in the fasted state, in general, time to reach peak plasma concentration was similar across the entire age group and occurred 0.5 hours to 2 hours postdose.
Pregabalin C\textsubscript{max} and AUC parameters increased in a linear manner with increasing dose within each age group. The AUC was lower by 30\% in paediatric patients below a weight of 30 kg due to an increased body weight adjusted clearance of 43\% for these patients in comparison to patients weighing ≥30 kg.

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

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

Pregabalin pharmacokinetics in patients younger than 3 months old have not been studied (see sections 4.2, 4.8 and 5.1).

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 Table 1).

Breast-feeding mothers
The pharmacokinetics of 150 mg pregabalin given every 12 hours (300 mg daily dose) was evaluated in 10 lactating women who were at least 12 weeks postpartum. Lactation had little to no influence on pregabalin pharmacokinetics. Pregabalin was excreted into breast milk with average steady-state concentrations approximately 76\% of those in maternal plasma. The estimated infant dose from breast milk (assuming mean milk consumption of 150 ml/kg/day) of women receiving 300 mg/day or the maximum dose of 600 mg/day would be 0.31 or 0.62 mg/kg/day, respectively. These estimated doses are approximately 7\% of the total daily maternal dose on a mg/kg basis.

5.3 Preclinical safety data

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 ≥ 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 \textit{in vitro} and \textit{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

Capsule content
Pregelatinised maize starch
Maize starch
Talc

Capsule shell
Gelatin
Titanium dioxide (E171)
Iron oxide yellow (E172)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC//Alu blister.

Pack sizes:
Blister packs: 21, 28, 84 or 100 hard capsules
Blister packs (unit dose): 84 x 1 or 100 x 1 hard capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.
7. MARKETING AUTHORISATION HOLDER

Sandoz GmbH
Biochemiestrasse 10
A-6250 Kundl
Austria

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1011/057-062

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 June 2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.
1. **NAME OF THE MEDICINAL PRODUCT**

Pregabalin Sandoz 225 mg hard capsules

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each hard capsule contains 225 mg of pregabalin.

For the full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Hard capsule. Pale orange opaque cap and white opaque body, capsule size 1 (19.4 mm x 6.9 mm), filled with white to nearly white coloured powder.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

- **Neuropathic pain**
  Pregabalin Sandoz is indicated for the treatment of peripheral and central neuropathic pain in adults.

- **Epilepsy**
  Pregabalin Sandoz is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.

- **Generalised Anxiety Disorder**
  Pregabalin Sandoz 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 individualised according to creatinine clearance (CLcr), as indicated in Table 1 determined using the following formula:

\[
CL_{\text{cr}}(\text{ml/min}) = \frac{1.23 \times [140 - \text{age (years)}] \times \text{weight (kg)}}{\text{serum creatinine (\mumol/l)}} (\times 0.85 \text{ for female patients})
\]

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**

<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>Starting dose (mg/day)</td>
<td>Maximum dose (mg/day)</td>
<td></td>
</tr>
<tr>
<td>≥ 60</td>
<td>150</td>
<td>600</td>
</tr>
<tr>
<td>≥ 30 - &lt; 60</td>
<td>75</td>
<td>300</td>
</tr>
<tr>
<td>≥ 15 - &lt; 30</td>
<td>25 – 50</td>
<td>150</td>
</tr>
<tr>
<td>&lt; 15</td>
<td>25</td>
<td>75</td>
</tr>
<tr>
<td>Supplementary dosage following haemodialysis (mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>100</td>
<td>Single dose+</td>
</tr>
</tbody>
</table>

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 (see section 5.2).

*Paediatric population*
The safety and efficacy of pregabalin in children below the age of 12 years and in adolescents (12-17 years of age) have not been established. Currently available data are described in section 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

**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**
Pregabalin Sandoz may be taken with or without food. Pregabalin Sandoz is for oral use only.

### 4.3 Contraindications

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

### 4.4 Special warnings and precautions for use

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

**Hypersensitivity reactions**
There have been reports in the postmarketing experience of hypersensitivity reactions, including cases of angioedema. Pregabalin should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper 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 postmarketing reports of loss of consciousness, confusion and mental impairment. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medicinal product.

**Vision-related effects**
In controlled trials, a higher proportion of patients treated with pregabalin reported blurred vision than did patients treated with placebo which resolved in a majority of cases with continued dosing. In the clinical studies 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 postmarketing experience, visual adverse reactions have also been reported, including loss of vision, visual blurring or other changes of visual acuity, many of which were transient. Discontinuation of pregabalin may result in resolution or improvement of these visual symptoms.

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

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

**Withdrawal symptoms**
After discontinuation of short-term and long-term treatment with pregabalin, withdrawal symptoms have been observed in some patients. The following events have been mentioned: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, nervousness, depression, pain, convulsion, hyperhidrosis and dizziness, suggestive of physical dependence. The patient should be informed about this at the start of the treatment.

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

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

**Congestive heart failure**

There have been postmarketing reports of congestive heart failure in some patients receiving pregabalin. These reactions are mostly seen in elderly cardiovascular compromised patients during pregabalin treatment for a neuropathic indication. Pregabalin should be used with caution in these patients. Discontinuation of pregabalin may resolve the reaction.

**Treatment of central 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 postmarketing reports of events related to reduced lower gastrointestinal tract function (e.g. intestinal obstruction, paralytic ileus, constipation) when pregabalin was co-administered with medications that have the potential to produce constipation, such as opioid analgesics. When pregabalin and opioids will be used in combination, measures to prevent constipation may be considered (especially in female patients and elderly).

**Misuse, abuse potential or dependence**

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

**Encephalopathy**

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

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 controlled clinical trials, multiple oral doses of pregabalin co-administered with oxycodone, lorazepam, or ethanol did not result in clinically important effects on respiration. In the postmarketing experience, there are reports of respiratory failure and coma in patients taking pregabalin and other central nervous system (CNS) depressant medicinal products. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone.

**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 in males and females**
As the potential risk for humans is unknown, effective contraception must be used in women of childbearing potential.

**Pregnancy**
There are no adequate data from the use of pregabalin in pregnant women.

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

Pregabalin Sandoz 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 Sandoz may have minor or moderate influence on the ability to drive and use machines. Pregabalin Sandoz 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 program involved over 8900 patients 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 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 (≥ 1/10); common (≥ 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

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse drug reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Nasopharyngitis</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Neutropaenia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td><em>Hypersensitivity</em></td>
</tr>
<tr>
<td>Rare</td>
<td><em>Angioedema, allergic reaction</em></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Appetite increased</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Anorexia, hypoglycaemia</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
</tr>
<tr>
<td>-----------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td><strong>Common</strong></td>
<td>Euphoric mood, confusion, irritability, disorientation, insomnia, libido decreased</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Hallucination, panic attack, restlessness, agitation, depression, depressed mood, elevated mood, aggression, mood swings, depersonalisation, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Disinhibition</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very Common</strong></td>
<td>Dizziness, somnolence, headache</td>
</tr>
<tr>
<td><strong>Common</strong></td>
<td>Ataxia, coordination abnormal, tremor, dysarthria, amnesia, memory impairment, disturbance in attention, paraesthesia, hypoaesthesia, sedation, balance disorder, lethargy</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>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</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Convulsions, parosmia, hypokinesia, dysgraphia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Eye disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
<td>Vision blurred, diplopia</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Peripheral vision loss, visual disturbance, eye swelling, visual field defect, visual acuity reduced, eye pain, asthenopia, photopsia, dry eye, laceration increased, eye irritation</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Vision loss, keratitis, oscillopsia, altered visual depth perception, mydriasis, strabismus, visual brightness</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ear and labyrinth disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
<td>Vertigo</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Hyperacusis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiac disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
<td>Tachycardia, atrioventricular block first degree, sinus bradycardia, congestive heart failure</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>QT prolongation, sinus tachycardia, sinus arrhythmia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
<td>Hypotension, hypertension, hot flushes, flushing, peripheral coldness</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiratory, thoracic and mediastinal disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
<td>Dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Pulmonary oedema, throat tightness,</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
<td>Vomiting, nausea, constipation, diarrhoea, flatulence, abdominal</td>
</tr>
<tr>
<td><strong>distension, dry mouth</strong></td>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
<td></td>
</tr>
</tbody>
</table>

**Uncommon**
Gastrooesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral

**Rare**
Ascites, pancreatitis, *swollen tongue*, dysphagia

### Skin and subcutaneous tissue disorders

**Uncommon**
Rash papular, urticaria, hyperhidrosis, *pruritus*

**Rare**
Stevens Johnson syndrome, cold sweat

### Musculoskeletal and connective tissue disorders

**Common**
Muscle cramp, arthralgia, back pain, pain in limb, cervical spasm

**Uncommon**
Joint swelling, myalgia, muscle twitching, neck pain, muscle stiffness

**Rare**
Rhabdomyolysis

### Renal and urinary disorders

**Uncommon**
Urinary incontinence, dysuria

**Rare**
Renal failure, oliguria, *urinary retention*

### Reproductive system and breast disorders

**Common**
Erectile dysfunction

**Uncommon**
Sexual dysfunction, ejaculation delayed, dysmenorrhoea, breast pain

**Rare**
Amenorrhoea, breast discharge, breast enlargement, *gynaecomastia*

### General disorders and administration site conditions

**Common**
Oedema peripheral, oedema, gait abnormal, fall, feeling drunk, feeling abnormal, fatigue

**Uncommon**
Generalised oedema, *face oedema*, chest tightness, pain, pyrexia, thirst, chills, asthenia

### Investigations

**Common**
Weight increased

**Uncommon**
Blood creatine phosphokinase increased, alanine aminotransferase increased, aspartate aminotransferase 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, suggestive of physical dependence. The patient should be informed about this at the start of the treatment.

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

**Paediatric population**
The pregabalin safety profile observed in two paediatric studies (pharmacokinetic and tolerability study, n=65; 1 year open label follow on safety study, n=54) was similar to that observed in the adult studies (see sections 4.2, 5.1 and 5.2).

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

**4.9 Overdose**

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

In rare occasions, cases of coma have been reported.

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

**5. PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

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

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

**Mechanism of action**
Pregabalin binds to an auxiliary subunit (α2-δ 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 BID or 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.

Paediatric population
The efficacy and safety of pregabalin as adjunctive treatment for epilepsy in paediatric 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 (n=65) were similar to those observed in adults. Results of a 1 year open label safety study in 54 paediatric patients from 3 months to 16 years of age with epilepsy indicate that the adverse events of pyrexia and upper respiratory infections were observed more frequently than in adult studies (see sections 4.2, 4.8 and 5.2).

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

Generalised Anxiety Disorder
Pregabalin has been studied in 6 controlled trials of 4-6 week duration, an elderly study of 8 week duration and a long-term relapse prevention study with a double blind relapse prevention phase of 6 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 $C_{\text{max}}$ by approximately 25-30% and a delay in $t_{\text{max}}$ to approximately 2.5 hours. However, administration of pregabalin with food has no clinically significant effect on the extent of pregabalin absorption.
Distribution
In preclinical studies, pregabalin has been shown to cross the blood brain barrier in mice, rats, and monkeys. Pregabalin has been shown to cross the placenta in rats and is present in the milk of lactating rats. In humans, the apparent volume of distribution of pregabalin following oral administration is approximately 0.56 l/kg. Pregabalin is not bound to plasma proteins.

Biotransformation
Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabelled pregabalin, approximately 98% of the radioactivity recovered in the urine was unchanged pregabalin. The N-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0.9% of the dose. In preclinical studies, there was no indication of racemisation of pregabalin S-enantiomer to the R-enantiomer.

Elimination
Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. Pregabalin mean elimination half-life is 6.3 hours. Pregabalin plasma clearance and renal clearance are directly proportional to creatinine clearance (see section 5.2 Renal impairment).

Dose adjustment in patients with reduced renal function or undergoing haemodialysis is necessary (see section 4.2 Table 1).

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

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

Renal impairment
Pregabalin clearance is directly proportional to creatinine clearance. In addition, pregabalin is effectively removed from plasma by haemodialysis (following a 4 hour haemodialysis treatment plasma pregabalin concentrations are reduced by approximately 50%). Because renal elimination is the major elimination pathway, dose reduction in patients with renal impairment and dose supplementation following haemodialysis is necessary (see section 4.2 Table 1).

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

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

After oral administration of pregabalin in paediatric patients in the fasted state, in general, time to reach peak plasma concentration was similar across the entire age group and occurred 0.5 hours to 2 hours postdose.
Pregabalin $C_{\text{max}}$ and AUC parameters increased in a linear manner with increasing dose within each age group. The AUC was lower by 30% in paediatric patients below a weight of 30 kg due to an increased body weight adjusted clearance of 43% for these patients in comparison to patients weighing ≥30 kg.

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

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

Pregabalin pharmacokinetics in patients younger than 3 months old have not been studied (see sections 4.2, 4.8 and 5.1).

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 Table 1).

Breast-feeding mothers
The pharmacokinetics of 150 mg pregabalin given every 12 hours (300 mg daily dose) was evaluated in 10 lactating women who were at least 12 weeks postpartum. Lactation had little to no influence on pregabalin pharmacokinetics. Pregabalin was excreted into breast milk with average steady-state concentrations approximately 76% of those in maternal plasma. The estimated infant dose from breast milk (assuming mean milk consumption of 150 ml/kg/day) of women receiving 300 mg/day or the maximum dose of 600 mg/day would be 0.31 or 0.62 mg/kg/day, respectively. These estimated doses are approximately 7% of the total daily maternal dose on a mg/kg basis.

5.3 Preclinical safety data
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 ≥ 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

Capsule content
Pregelatinised maize starch
Maize starch
Talc

Capsule shell
Gelatin
Titanium dioxide (E171)
Iron oxide yellow (E172)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC//Alu blister.

Pack sizes:
Blister packs: 14, 56, 70, 84, 100 or 120 hard capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER
8. MARKETING AUTHORITY NUMBER(S)

EU/1/15/1011/063-068

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORITY

Date of first authorisation: 19 June 2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.
1. NAME OF THE MEDICINAL PRODUCT

Pregabalin Sandoz 300 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 300 mg of pregabalin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.
Red opaque cap and pale yellow-brown opaque body, capsule size 0 (21.7 mm x 7.6 mm), filled with white to nearly white coloured powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Epilepsy
Pregabalin Sandoz is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.

Generalised Anxiety Disorder
Pregabalin Sandoz 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 individualised according to creatinine clearance (CLcr), as indicated in Table 1 determined using the following formula:

\[
CLr (\text{ml/min}) = \frac{1.23 \times [140 - \text{age (years)}] \times \text{weight (kg)}}{\text{serum creatinine (µmol/l)}} \times 0.85 \text{ for female patients}
\]

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**

<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></td>
<td>Starting dose (mg/day)</td>
<td>Maximum dose (mg/day)</td>
</tr>
<tr>
<td>≥ 60</td>
<td>150</td>
<td>600</td>
</tr>
<tr>
<td>≥ 30 - &lt; 60</td>
<td>75</td>
<td>300</td>
</tr>
<tr>
<td>≥ 15 - &lt; 30</td>
<td>25 – 50</td>
<td>150</td>
</tr>
<tr>
<td>&lt; 15</td>
<td>25</td>
<td>75</td>
</tr>
<tr>
<td>Supplementary dosage following haemodialysis (mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>100</td>
</tr>
</tbody>
</table>

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 (see section 5.2).

**Paediatric population**
The safety and efficacy of pregabalin in children below the age of 12 years and in adolescents (12-17 years of age) have not been established. Currently available data are described in section 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

**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
Pregabalin Sandoz may be taken with or without food.
Pregabalin Sandoz is for oral use only.

### 4.3 Contraindications

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

### 4.4 Special warnings and precautions for use

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

**Hypersensitivity reactions**
There have been reports in the postmarketing experience of hypersensitivity reactions, including cases of angioedema. Pregabalin should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper 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 postmarketing reports of loss of consciousness, confusion and mental impairment. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medicinal product.

**Vision-related effects**
In controlled trials, a higher proportion of patients treated with pregabalin reported blurred vision than did patients treated with placebo which resolved in a majority of cases with continued dosing. In the clinical studies 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 postmarketing experience, visual adverse reactions have also been reported, including loss of vision, visual blurring or other changes of visual acuity, many of which were transient. Discontinuation of pregabalin may result in resolution or improvement of these visual symptoms.

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

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

**Withdrawal symptoms**
After discontinuation of short-term and long-term treatment with pregabalin, withdrawal symptoms have been observed in some patients. The following events have been mentioned: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, nervousness, depression, pain, convulsion, hyperhidrosis and dizziness, suggestive of physical dependence. The patient should be informed about this at the start of the treatment.

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

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

**Congestive heart failure**
There have been postmarketing reports of congestive heart failure in some patients receiving pregabalin. These reactions are mostly seen in elderly cardiovascular compromised patients during pregabalin treatment for a neuropathic indication. Pregabalin should be used with caution in these patients. Discontinuation of pregabalin may resolve the reaction.

**Treatment of central 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).

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

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

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 controlled clinical trials, multiple oral doses of pregabalin co-administered with oxycodone, lorazepam, or ethanol did not result in clinically important effects on respiration. In the postmarketing experience, there are reports of respiratory failure and coma in patients taking pregabalin and other central nervous system (CNS) depressant medicinal products. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone.

**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 in males and females**
As the potential risk for humans is unknown, effective contraception must be used in women of childbearing potential.

**Pregnancy**
There are no adequate data from the use of pregabalin in pregnant women.

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

Pregabalin Sandoz 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 Sandoz may have minor or moderate influence on the ability to drive and use machines. Pregabalin Sandoz 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 program involved over 8900 patients 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 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 (≥ 1/10); common (≥ 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**

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse drug reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Nasopharyngitis</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Neutropaenia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td><strong>Hypersensitivity</strong></td>
</tr>
<tr>
<td>Rare</td>
<td><strong>Angioedema, allergic reaction</strong></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Appetite increased</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Anorexia, hypoglycaemia</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Common</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>Euphoric mood, confusion, irritability, disorientation, insomnia, libido decreased</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Very Common Dizziness, somnolence, headache</td>
</tr>
<tr>
<td></td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Ataxia, coordination abnormal, tremor, dysarthria, amnesia, memory impairment, disturbance in attention, paraesthesia, hypoaesthesia, sedation, balance disorder, lethargy</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Convulsions, parosmia, hypokinesia, dysgraphia</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Vision blurred, diplopia</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Peripheral vision loss, visual disturbance, eye swelling, visual field defect, visual acuity reduced, eye pain, asthenopia, photopsia, dry eye, laceration increased, eye irritation</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Vision loss, keratitis, oscillopsia, altered visual depth perception, mydriasis, strabismus, visual brightness</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Vertigo</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Hyperacusis</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Tachycardia, atrioventricular block first degree, sinus bradycardia, congestive heart failure</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>QT prolongation, sinus tachycardia, sinus arrhythmia</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Hypotension, hypertension, hot flushes, flushing, peripheral coldness</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Pulmonary oedema, throat tightness,</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Vomiting, nausea, constipation, diarrhoea, flatulence, abdominal</td>
</tr>
<tr>
<td>Adverse Reaction</td>
<td>Frequency</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>distension, dry mouth</td>
<td></td>
</tr>
<tr>
<td>Uncommon Gastrooesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral</td>
<td></td>
</tr>
<tr>
<td>Rare Ascites, pancreatitis, swollen tongue, dysphagia</td>
<td></td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon Rash papular, urticaria, hyperhidrosis, pruritus</td>
<td></td>
</tr>
<tr>
<td>Rare Stevens Johnson syndrome, cold sweat</td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common Muscle cramp, arthralgia, back pain, pain in limb, cervical spasm</td>
<td></td>
</tr>
<tr>
<td>Uncommon Joint swelling, myalgia, muscle twitching, neck pain, muscle stiffness</td>
<td></td>
</tr>
<tr>
<td>Rare Rhabdomyolysis</td>
<td></td>
</tr>
<tr>
<td><strong>Renal and urinary disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon Urinary incontinence, dysuria</td>
<td></td>
</tr>
<tr>
<td>Rare Renal failure, oliguria, urinary retention</td>
<td></td>
</tr>
<tr>
<td><strong>Reproductive system and breast disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common Erectile dysfunction</td>
<td></td>
</tr>
<tr>
<td>Uncommon Sexual dysfunction, ejaculation delayed, dysmenorrhoea, breast pain</td>
<td></td>
</tr>
<tr>
<td>Rare Amenorrhoea, breast discharge, breast enlargement, gynaecomastia</td>
<td></td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Common Oedema peripheral, oedema, gait abnormal, fall, feeling drunk, feeling abnormal, fatigue</td>
<td></td>
</tr>
<tr>
<td>Uncommon Generalised oedema, face oedema, chest tightness, pain, pyrexia, thirst, chills, asthenia</td>
<td></td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
</tr>
<tr>
<td>Common Weight increased</td>
<td></td>
</tr>
<tr>
<td>Uncommon Blood creatine phosphokinase increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood glucose increased, platelet count decreased, blood creatinine increased, blood potassium decreased, weight decreased</td>
<td></td>
</tr>
<tr>
<td>Rare White blood cell count decreased</td>
<td></td>
</tr>
</tbody>
</table>

After discontinuation of short-term and long-term treatment with pregabalin withdrawal symptoms have been observed in some patients. The following reactions have been mentioned: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, convulsions, nervousness, depression, pain, hyperhidrosis and dizziness, suggestive of physical dependence. The patient should be informed about this at the start of the treatment.

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

**Paediatric population**
The pregabalin safety profile observed in two paediatric studies (pharmacokinetic and tolerability study, n=65; 1 year open label follow on safety study, n=54) was similar to that observed in the adult studies (see sections 4.2, 5.1 and 5.2).

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 **Overdose**

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

In rare occasions, cases of coma have been reported.

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

5. **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**

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

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

**Mechanism of action**
Pregabalin binds to an auxiliary subunit (α2-δ 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 BID or 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.

Paediatric population
The efficacy and safety of pregabalin as adjunctive treatment for epilepsy in paediatric 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 (n=65) were similar to those observed in adults. Results of a 1 year open label safety study in 54 paediatric patients from 3 months to 16 years of age with epilepsy indicate that the adverse events of pyrexia and upper respiratory infections were observed more frequently than in adult studies (see sections 4.2, 4.8 and 5.2).

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

Generalised Anxiety Disorder
Pregabalin has been studied in 6 controlled trials of 4-6 week duration, an elderly study of 8 week duration and a long-term relapse prevention study with a double blind relapse prevention phase of 6 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 \( C_{\text{max}} \) by approximately 25-30% and a delay in \( t_{\text{max}} \) to approximately 2.5 hours. However, administration of pregabalin with food has no clinically significant effect on the extent of pregabalin absorption.
Distribution
In preclinical studies, pregabalin has been shown to cross the blood brain barrier in mice, rats, and monkeys. Pregabalin has been shown to cross the placenta in rats and is present in the milk of lactating rats. In humans, the apparent volume of distribution of pregabalin following oral administration is approximately 0.56 l/kg. Pregabalin is not bound to plasma proteins.

Biotransformation
Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabelled pregabalin, approximately 98% of the radioactivity recovered in the urine was unchanged pregabalin. The N-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0.9% of the dose. In preclinical studies, there was no indication of racemisation of pregabalin S-enantiomer to the R-enantiomer.

Elimination
Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. Pregabalin mean elimination half-life is 6.3 hours. Pregabalin plasma clearance and renal clearance are directly proportional to creatinine clearance (see section 5.2 Renal impairment).

Dose adjustment in patients with reduced renal function or undergoing haemodialysis is necessary (see section 4.2 Table 1).

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

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

Renal impairment
Pregabalin clearance is directly proportional to creatinine clearance. In addition, pregabalin is effectively removed from plasma by haemodialysis (following a 4 hour haemodialysis treatment plasma pregabalin concentrations are reduced by approximately 50%). Because renal elimination is the major elimination pathway, dose reduction in patients with renal impairment and dose supplementation following haemodialysis is necessary (see section 4.2 Table 1).

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

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

After oral administration of pregabalin in paediatric patients in the fasted state, in general, time to reach peak plasma concentration was similar across the entire age group and occurred 0.5 hours to 2 hours postdose.
Pregabalin $C_{\text{max}}$ and AUC parameters increased in a linear manner with increasing dose within each age group. The AUC was lower by 30% in paediatric patients below a weight of 30 kg due to an increased body weight adjusted clearance of 43% for these patients in comparison to patients weighing $\geq30$ kg.

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

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

Pregabalin pharmacokinetics in patients younger than 3 months old have not been studied (see sections 4.2, 4.8 and 5.1).

Elderly (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 Table 1).

Breast-feeding mothers
The pharmacokinetics of 150 mg pregabalin given every 12 hours (300 mg daily dose) was evaluated in 10 lactating women who were at least 12 weeks postpartum. Lactation had little to no influence on pregabalin pharmacokinetics. Pregabalin was excreted into breast milk with average steady-state concentrations approximately 76% of those in maternal plasma. The estimated infant dose from breast milk (assuming mean milk consumption of 150 ml/kg/day)of women receiving 300 mg/day or the maximum dose of 600 mg/day would be 0.31 or 0.62 mg/kg/day, respectively. These estimated doses are approximately 7% of the total daily maternal dose on a mg/kg basis.

5.3 Preclinical safety data

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

Capsule content
Pregelatinised maize starch
Maize starch
Talc

Capsule shell
Gelatin
Titanium dioxide (E171)
Iron oxide yellow (E172)
Iron oxide red (E172)
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.
After first opening of the container: 6 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC/Alu blister.
HDPE container with PP screw cap.

Pack sizes:
Blister packs: 14, 21, 28, 56, 70, 84 (2 x 42), 100 (2 x 50) or 120 (2 x 60) hard capsules
Blister packs (unit dose): 56 x 1, 84 x 1 (2 x 42), 100 x 1 (2 x 50) or 210 x 1 (3 x 70) hard capsules
Container packs: 100, 200 or 250 hard capsules

Not all pack sizes may be marketed.
6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Sandoz GmbH
Biochemiestrasse 10
A-6250 Kundl
Austria

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1011/069-083

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 June 2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.
ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT
A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Lek Pharmaceuticals d.d.
Verovškova 57
1526 Ljubljana
Slovenia

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Pregabalin Sandoz 25 mg hard capsules
pregabalin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 25 mg of pregabalin.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 hard capsules
28 hard capsules
56 hard capsules
70 hard capsules
84 hard capsules
100 hard capsules
120 hard capsules
56 x 1 hard capsules
84 x 1 hard capsules
100 x 1 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
9. **SPECIAL STORAGE CONDITIONS**

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

   Sandoz GmbH
   Biochemiestrasse 10
   6250 Kundl
   Austria

12. **MARKETING AUTHORISATION NUMBER(S)**

   EU/1/15/1011/001-010

13. **BATCH NUMBER**

   Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

   Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

   Pregabalin Sandoz 25 mg
**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTERS**

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>1.</td>
<td><strong>NAME OF THE MEDICINAL PRODUCT</strong></td>
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<tr>
<td></td>
<td>Pregabalin Sandoz 25 mg hard capsules</td>
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<tr>
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<td></td>
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<td>4.</td>
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<td></td>
<td>Lot</td>
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<tr>
<td>5.</td>
<td><strong>OTHER</strong></td>
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</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON FOR CONTAINER AND LABEL FOR CONTAINER

1. **NAME OF THE MEDICINAL PRODUCT**

Pregabalin Sandoz 25 mg hard capsules
pregabalin

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each hard capsule contains 25 mg of pregabalin.

3. **LIST OF EXCIPIENTS**

4. **PHARMACEUTICAL FORM AND CONTENTS**

200 hard capsules

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.
Oral use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

EXP
Use within 6 months after first opening.

9. **SPECIAL STORAGE CONDITIONS**

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**
11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sandoz GmbH
Biochemiestrasse 10
6250 Kundl
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1011/084

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Outer carton: Pregabalin Sandoz 25 mg
### PARTICULARS TO APPEAR ON THE OUTER PACKAGING

**OUTER CARTON FOR BLISTER**

#### 1. NAME OF THE MEDICINAL PRODUCT

Pregabalin Sandoz 50 mg hard capsules
pregabalin

#### 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 50 mg of pregabalin.

#### 3. LIST OF EXCIPIENTS

#### 4. PHARMACEUTICAL FORM AND CONTENTS

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<thead>
<tr>
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<tr>
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<tr>
<td>21</td>
<td>hard capsules</td>
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<td>84 x 1</td>
<td>hard capsules</td>
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#### 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

#### 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

#### 7. OTHER SPECIAL WARNING(S), IF NECESSARY

#### 8. EXPIRY DATE

EXP

#### 9. SPECIAL STORAGE CONDITIONS
### 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

### 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<table>
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<th>Sandoz GmbH</th>
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<tr>
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<tr>
<td>6250 Kundl</td>
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<td>Austria</td>
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### 12. MARKETING AUTHORISATION NUMBER(S)

- EU/1/15/1011/011-017

### 13. BATCH NUMBER

- Lot

### 14. GENERAL CLASSIFICATION FOR SUPPLY

- Medicinal product subject to medical prescription.

### 15. INSTRUCTIONS ON USE

### 16. INFORMATION IN BRAILLE

- Pregabalin Sandoz 50 mg
**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

### BLISTERS

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<thead>
<tr>
<th>1. <strong>NAME OF THE MEDICINAL PRODUCT</strong></th>
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<tbody>
<tr>
<td>Pregabalin Sandoz 50 mg hard capsules</td>
</tr>
<tr>
<td>pregabalin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. <strong>NAME OF THE MARKETING AUTHORISATION HOLDER</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sandoz</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. <strong>EXPIRY DATE</strong></th>
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</thead>
<tbody>
<tr>
<td>EXP</td>
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<table>
<thead>
<tr>
<th>4. <strong>BATCH NUMBER</strong></th>
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<tbody>
<tr>
<td>Lot</td>
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<table>
<thead>
<tr>
<th>5. <strong>OTHER</strong></th>
</tr>
</thead>
</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON FOR CONTAINER AND LABEL FOR CONTAINER

1. NAME OF THE MEDICINAL PRODUCT
Pregabalin Sandoz 50 mg hard capsules
pregabalin

2. STATEMENT OF ACTIVE SUBSTANCE(S)
Each hard capsule contains 50 mg of pregabalin.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS
200 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION
Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN
Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE
EXP
Use within 6 months after first opening.

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
<table>
<thead>
<tr>
<th>11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sandoz GmbH</td>
</tr>
<tr>
<td>Biochemiestrasse 10</td>
</tr>
<tr>
<td>6250 Kundl</td>
</tr>
<tr>
<td>Austria</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>12. MARKETING AUTHORISATION NUMBER(S)</th>
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<tr>
<td>EU/1/15/1011/085</td>
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<table>
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<tr>
<th>13. BATCH NUMBER</th>
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<tbody>
<tr>
<td>Lot</td>
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<table>
<thead>
<tr>
<th>14. GENERAL CLASSIFICATION FOR SUPPLY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicinal product subject to medical prescription.</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>15. INSTRUCTIONS ON USE</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>16. INFORMATION IN BRAILLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outer carton: Pregabalin Sandoz 50 mg</td>
</tr>
</tbody>
</table>
**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**OUTER CARTON FOR CONTAINER AND LABEL FOR CONTAINER**

1. **NAME OF THE MEDICINAL PRODUCT**
   
Pregabalin Sandoz 75 mg hard capsules
pregabalin

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**
   
Each hard capsule contains 75 mg of pregabalin.

3. **LIST OF EXCIPIENTS**

4. **PHARMACEUTICAL FORM AND CONTENTS**
   
100 hard capsules
200 hard capsules
250 hard capsules

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**
   
Read the package leaflet before use.
Oral use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**
   
Keep out of the sight and reach of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**
   
EXP
Use within 6 months after first opening.

9. **SPECIAL STORAGE CONDITIONS**
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sandoz GmbH
Biochemiestrasse 10
6250 Kundl
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1011/031-033

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Outer carton: Pregabalin Sandoz 75 mg
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Pregabalin Sandoz 75 mg hard capsules
pregabalin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 75 mg of pregabalin.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 hard capsules
21 hard capsules
28 hard capsules
56 hard capsules
70 hard capsules
84 hard capsules
100 hard capsules
120 hard capsules
14 x 1 hard capsules
56 x 1 hard capsules
84 x 1 hard capsules
100 x 1 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE
9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sandoz GmbH
Biochemiestrasse 10
6250 Kundl
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1011/018-029

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pregabalin Sandoz 75 mg
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER WRAPPER LABEL ON MULTIPACKS WRAPPED IN FOIL (INCLUDING THE BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Pregabalin Sandoz 75 mg hard capsules
pregabalin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 75 mg of pregabalin.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 210 x 1 (3 packs of 70 x 1) hard capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
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<td>Sandoz GmbH</td>
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<td>12. MARKETING AUTHORISATION NUMBER(S)</td>
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<td>13. BATCH NUMBER</td>
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<tr>
<td>Medicinal product subject to medical prescription.</td>
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<td>15. INSTRUCTIONS ON USE</td>
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<td></td>
</tr>
<tr>
<td>16. INFORMATION IN BRAILLE</td>
</tr>
<tr>
<td></td>
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</tbody>
</table>
### 1. NAME OF THE MEDICINAL PRODUCT

Pregabalin Sandoz 75 mg hard capsules
pregabalin

### 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 75 mg of pregabalin.

### 3. LIST OF EXCIPIENTS

### 4. PHARMACEUTICAL FORM AND CONTENTS

70 x 1 hard capsules. Component of a multipack, can’t be sold separately.

### 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

### 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

### 7. OTHER SPECIAL WARNING(S), IF NECESSARY

### 8. EXPIRY DATE

EXP

### 9. SPECIAL STORAGE CONDITIONS

### 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
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<th>11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</th>
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<td>Lot</td>
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<th>14. GENERAL CLASSIFICATION FOR SUPPLY</th>
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<tbody>
<tr>
<td>Medicinal product subject to medical prescription.</td>
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| 15. INSTRUCTIONS ON USE                                   |

<table>
<thead>
<tr>
<th>16. INFORMATION IN BRAILLE</th>
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</thead>
<tbody>
<tr>
<td>Pregabalin Sandoz 75 mg</td>
</tr>
</tbody>
</table>
### MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

#### BLISTERS

1. **NAME OF THE MEDICINAL PRODUCT**
   - Pregabalin Sandoz 75 mg hard capsules
   - pregabalin

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**
   - Sandoz

3. **EXPIRY DATE**
   - EXP

4. **BATCH NUMBER**
   - Lot

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

Pregabalin Sandoz 100 mg hard capsules  
**pregabalin**

### 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 100 mg of pregabalin.

### 3. LIST OF EXCIPIENTS

### 4. PHARMACEUTICAL FORM AND CONTENTS

- 14 hard capsules
- 21 hard capsules
- 28 hard capsules
- 56 hard capsules
- 84 hard capsules
- 100 hard capsules
- 84 x 1 hard capsules
- 100 x 1 hard capsules

### 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.  
**Oral use.**

### 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

### 7. OTHER SPECIAL WARNING(S), IF NECESSARY

### 8. EXPIRY DATE

**EXP**
9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sandoz GmbH
Biochemiestrasse 10
6250 Kundl
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1011/034-041

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pregabalin Sandoz 100 mg
### MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

#### BLISTERS

1. **NAME OF THE MEDICINAL PRODUCT**

   Pregabalin Sandoz 100 mg hard capsules

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**

   Sandoz

3. **EXPIRY DATE**

   EXP

4. **BATCH NUMBER**

   Lot

5. **OTHER**
1. NAME OF THE MEDICINAL PRODUCT

Pregabalin Sandoz 150 mg hard capsules
pregabalin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 150 mg of pregabalin.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

100 hard capsules
200 hard capsules
250 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Use within 6 months after first opening.

9. SPECIAL STORAGE CONDITIONS
<table>
<thead>
<tr>
<th>10.</th>
<th>SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.</td>
<td>NAME AND ADDRESS OF THE MARKETING AUTHORITY[ATION HOLDER</td>
</tr>
</tbody>
</table>
|     | Sandoz GmbH  
Biochemiestrasse 10  
6250 Kundl  
Austria |
| 12. | MARKETING AUTHORIZATION NUMBER(S) |
|     | EU/1/15/1011/054-056 |
| 13. | BATCH NUMBER |
|     | Lot |
| 14. | GENERAL CLASSIFICATION FOR SUPPLY |
|     | Medicinal product subject to medical prescription. |
| 15. | INSTRUCTIONS ON USE |
| 16. | INFORMATION IN BRAILLE |
|     | Outer carton: Pregabalin Sandoz 150 mg |
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Pregabalin Sandoz 150 mg hard capsules
pregabalin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 150 mg of pregabalin.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 hard capsules
21 hard capsules
28 hard capsules
56 hard capsules
70 hard capsules
84 hard capsules
100 hard capsules
120 hard capsules
56 x 1 hard capsules
84 x 1 hard capsules
100 x 1 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sandoz GmbH
Biochemiestrasse 10
6250 Kundl
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1011/042-052

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pregabalin Sandoz 150 mg
**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER WRAPPER LABEL ON MULTIPACKS WRAPPED IN FOIL (INCLUDING THE BLUE BOX)**

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregabalin Sandoz 150 mg hard capsules</td>
</tr>
<tr>
<td>pregabalin</td>
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<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each hard capsule contains 150 mg of pregabalin.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. LIST OF EXCIPIENTS</th>
</tr>
</thead>
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<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multipack: 210 x 1 (3 packs of 70 x 1) hard capsules</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
<tr>
<td>Oral use.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of the sight and reach of children.</td>
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<table>
<thead>
<tr>
<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
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<tr>
<th>8. EXPIRY DATE</th>
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<td>EXP</td>
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<table>
<thead>
<tr>
<th>9. SPECIAL STORAGE CONDITIONS</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</th>
</tr>
</thead>
</table>
**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Sandoz GmbH  
Biochemiestrasse 10  
6250 Kundl  
Austria

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/15/1011/053

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
MULTIPACKS – WITHOUT BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT
Pregabalin Sandoz 150 mg hard capsules
pregabalin

2. STATEMENT OF ACTIVE SUBSTANCE(S)
Each hard capsule contains 150 mg of pregabalin.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS
70 x 1 hard capsules. Component of a multipack, can’t be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION
Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT
OF THE SIGHT AND REACH OF CHILDREN
Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE
EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS
OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF
APPROPRIATE
11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sandoz GmbH
Biochemiestrasse 10
6250 Kundl
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1011/053

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pregabalin Sandoz 150 mg
### MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

#### BLISTERS

1. **NAME OF THE MEDICINAL PRODUCT**
   
   Pregabalin Sandoz 150 mg hard capsules  
   pregabalin

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**
   
   Sandoz

3. **EXPIRY DATE**
   
   Exp

4. **BATCH NUMBER**
   
   Lot

5. **OTHER**
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON FOR BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Pregabalin Sandoz 200 mg hard capsules
pregabalin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 200 mg of pregabalin.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

21 hard capsules
28 hard capsules
84 hard capsules
100 hard capsules
84 x 1 hard capsules
100 x 1 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS
<table>
<thead>
<tr>
<th>Section</th>
<th>Information</th>
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</thead>
<tbody>
<tr>
<td>10.</td>
<td><strong>SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</strong></td>
</tr>
<tr>
<td>11.</td>
<td><strong>NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</strong>&lt;br&gt;Sandoz GmbH&lt;br&gt;Biochemiestrasse 10&lt;br&gt;6250 Kundl&lt;br&gt;Austria</td>
</tr>
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<td>12.</td>
<td><strong>MARKETING AUTHORISATION NUMBER(S)</strong>&lt;br&gt;EU/1/15/1011/057-062</td>
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<tr>
<td>13.</td>
<td><strong>BATCH NUMBER</strong>&lt;br&gt;Lot</td>
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<tr>
<td>14.</td>
<td><strong>GENERAL CLASSIFICATION FOR SUPPLY</strong>&lt;br&gt;Medicinal product subject to medical prescription.</td>
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<tr>
<td>15.</td>
<td><strong>INSTRUCTIONS ON USE</strong></td>
</tr>
<tr>
<td>16.</td>
<td><strong>INFORMATION IN BRAILLE</strong>&lt;br&gt;Pregabalin Sandoz 200 mg</td>
</tr>
</tbody>
</table>
### MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

#### BLISTERS

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<tbody>
<tr>
<td><strong>1.</strong> NAME OF THE MEDICINAL PRODUCT</td>
<td>Pregabalin Sandoz 200 mg hard capsules pregnabalin</td>
</tr>
<tr>
<td><strong>2.</strong> NAME OF THE MARKETING AUTHORISATION HOLDER</td>
<td>Sandoz</td>
</tr>
<tr>
<td><strong>3.</strong> EXPIRY DATE</td>
<td>EXP</td>
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<tr>
<td><strong>4.</strong> BATCH NUMBER</td>
<td>Lot</td>
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<tr>
<td><strong>5.</strong> OTHER</td>
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</table>
### PARTICULARS TO APPEAR ON THE OUTER PACKAGING

**OUTER CARTON FOR BLISTER**

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
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<tbody>
<tr>
<td>Pregabalin Sandoz 225 mg hard capsules</td>
</tr>
<tr>
<td>pregabalin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each hard capsule contains 225 mg of pregabalin.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. LIST OF EXCIPIENTS</th>
</tr>
</thead>
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<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 hard capsules</td>
</tr>
<tr>
<td>56 hard capsules</td>
</tr>
<tr>
<td>70 hard capsules</td>
</tr>
<tr>
<td>84 hard capsules</td>
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<tr>
<td>100 hard capsules</td>
</tr>
<tr>
<td>120 hard capsules</td>
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<table>
<thead>
<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
<tr>
<td>Oral use.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of the sight and reach of children.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>8. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>9. SPECIAL STORAGE CONDITIONS</th>
</tr>
</thead>
</table>
10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

<table>
<thead>
<tr>
<th>Sandoz GmbH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemiestrasse 10</td>
</tr>
<tr>
<td>6250 Kundl</td>
</tr>
<tr>
<td>Austria</td>
</tr>
</tbody>
</table>

12. **MARKETING AUTHORISATION NUMBER(S)**

| EU/1/15/1011/063-068 |

13. **BATCH NUMBER**

| Lot |

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

| Pregabalin Sandoz 225 mg |
### BLISTERS

1. **NAME OF THE MEDICINAL PRODUCT**

   Pregabalin Sandoz 225 mg hard capsules  
pregabalin

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**

   Sandoz

3. **EXPIRY DATE**

   EXP

4. **BATCH NUMBER**

   Lot

5. **OTHER**
### PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

**OUTER CARTON FOR CONTAINER AND LABEL FOR CONTAINER**

### 1. NAME OF THE MEDICINAL PRODUCT

Pregabalin Sandoz 300 mg hard capsules  
pregabalin

### 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 300 mg of pregabalin.

### 3. LIST OF EXCIPIENTS

### 4. PHARMACEUTICAL FORM AND CONTENTS

100 hard capsules  
200 hard capsules  
250 hard capsules

### 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.  
Oral use.

### 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

### 7. OTHER SPECIAL WARNING(S), IF NECESSARY

### 8. EXPIRY DATE

EXP  
Use within 6 months after first opening.

### 9. SPECIAL STORAGE CONDITIONS
<table>
<thead>
<tr>
<th>10.</th>
<th>SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.</td>
<td>NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</td>
</tr>
</tbody>
</table>
| | Sandoz GmbH  
| | Biochemiestrasse 10  
| | 6250 Kundl  
<p>| | Austria |
| 12. | MARKETING AUTHORISATION NUMBER(S) |
| | EU/1/15/1011/081-083 |
| 13. | BATCH NUMBER |
| | Lot |
| 14. | GENERAL CLASSIFICATION FOR SUPPLY |
| | Medicinal product subject to medical prescription. |
| 15. | INSTRUCTIONS ON USE |
| 16. | INFORMATION IN BRAILLE |
| | Outer carton: Pregabalin Sandoz 300 mg |</p>
<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING</th>
</tr>
</thead>
<tbody>
<tr>
<td>OUTER CARTON FOR BLISTER</td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**

Pregabalin Sandoz 300 mg hard capsules
pregabalin

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each hard capsule contains 300 mg of pregabalin.

3. **LIST OF EXCIPIENTS**

4. **PHARMACEUTICAL FORM AND CONTENTS**

- 14 hard capsules
- 21 hard capsules
- 28 hard capsules
- 56 hard capsules
- 70 hard capsules
- 56 x 1 hard capsules

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.
Oral use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

EXP

9. **SPECIAL STORAGE CONDITIONS**
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sandoz GmbH
Biochemiestrasse 10
6250 Kundl
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1011/069-073
EU/1/15/1011/077

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pregabalin Sandoz 300 mg
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER WRAPPER LABEL ON MULTIPACKS WRAPPED IN FOIL (INCLUDING THE BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Pregabalin Sandoz 300 mg hard capsules
pregabalin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 300 mg of pregabalin.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 84 (2 packs of 42) hard capsules
Multipack: 100 (2 packs of 50) hard capsules
Multipack: 120 (2 packs of 60) hard capsules
Multipack: 84 x 1 (2 packs of 42 x 1) hard capsules
Multipack: 100 x 1 (2 packs of 50 x 1) hard capsules
Multipack: 210 x 1 (3 packs of 70 x 1) hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sandoz GmbH
Biochemiestrasse 10
6250 Kundl
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1011/074-076
EU/1/15/1011/078-080

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

MULTIPACKS – WITHOUT BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Pregabalin Sandoz 300 mg hard capsules
pregabalin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 300 mg of pregabalin.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

42 hard capsules. Component of a multipack, can’t be sold separately.
50 hard capsules. Component of a multipack, can’t be sold separately.
60 hard capsules. Component of a multipack, can’t be sold separately.
42 x 1 hard capsules. Component of a multipack, can’t be sold separately.
50 x 1 hard capsules. Component of a multipack, can’t be sold separately.
70 x 1 hard capsules. Component of a multipack, can’t be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sandoz GmbH
Biochemiestrasse 10
6250 Kundl
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1011/074-076
EU/1/15/1011/078-080

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pregabalin Sandoz 300 mg
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BLISTERS</strong></td>
<td></td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**
   
Pregabalin Sandoz 300 mg hard capsules
pregabalin

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**
   
Sandoz

3. **EXPIRY DATE**
   
EXP

4. **BATCH NUMBER**
   
Lot

5. **OTHER**
   

B. PACKAGE LEAFLET
Package leaflet: Information for the user

Pregabalin Sandoz 25 mg hard capsules
Pregabalin Sandoz 50 mg hard capsules
Pregabalin Sandoz 75 mg hard capsules
Pregabalin Sandoz 100 mg hard capsules
Pregabalin Sandoz 150 mg hard capsules
Pregabalin Sandoz 200 mg hard capsules
Pregabalin Sandoz 225 mg hard capsules
Pregabalin Sandoz 300 mg hard capsules

Pregabalin

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet
1. What Pregabalin Sandoz is and what it is used for
2. What you need to know before you take Pregabalin Sandoz
3. How to take Pregabalin Sandoz
4. Possible side effects
5. How to store Pregabalin Sandoz
6. Contents of the pack and other information

1. What Pregabalin Sandoz is and what it is used for

Pregabalin Sandoz belongs to a group of medicines used to treat epilepsy, neuropathic pain and Generalised Anxiety Disorder (GAD) in adults.

Peripheral and central neuropathic pain: Pregabalin Sandoz is used to treat long lasting pain caused by damage to the nerves. A variety of diseases can cause peripheral neuropathic pain, such as diabetes or shingles. Pain sensations may be described as hot, burning, throbbing, shooting, stabbing, sharp, cramping, aching, tingling, numbness, pins and needles. Peripheral and central neuropathic pain may also be associated with mood changes, sleep disturbance, fatigue (tiredness), and can have an impact on physical and social functioning and overall quality of life.

Epilepsy: Pregabalin Sandoz is used to treat a certain form of epilepsy (partial seizures with or without secondary generalisation) in adults. Your doctor will prescribe Pregabalin Sandoz for you to help treat your epilepsy when your current treatment is not controlling your condition. You should take Pregabalin Sandoz in addition to your current treatment. Pregabalin Sandoz is not intended to be used alone, but should always be used in combination with other anti-epileptic treatment.

Generalised Anxiety Disorder: Pregabalin Sandoz is used to treat Generalised Anxiety Disorder (GAD). The symptoms of GAD are prolonged excessive anxiety and worry that are difficult to control. GAD can also cause restlessness or feeling keyed up or on edge, being easily fatigued (tired), having difficulty concentrating or mind going blank, feeling irritable, having muscle tension or sleep disturbance. This is different to the stresses and strains of everyday life.
2. What you need to know before you take Pregabalin Sandoz

Do not take Pregabalin Sandoz
If you are allergic to pregabalin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or pharmacist before taking Lyrica.

- Some patients taking Pregabalin Sandoz have reported symptoms suggesting an allergic reaction. These symptoms include swelling of the face, lips, tongue, and throat, as well as diffuse skin rash. Should you experience any of these reactions, you should contact your physician immediately.

- Pregabalin Sandoz has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in elderly patients. Therefore, you should be careful until you are used to any effect the medicine might have.

- Pregabalin Sandoz may cause blurring or loss of vision, or other changes in eyesight, many of which are temporary. You should immediately tell your doctor if you experience any changes in your vision.

- Some patients with diabetes who gain weight while taking pregabalin may need an alteration in their diabetic medicines.

- Certain side effects may be more common, such as sleepiness, because patients with spinal cord injury may be taking other medicines to treat, for example, pain or spasticity, that have similar side effects to Pregabalin and the severity of these effects may be increased when taken together.

- There have been reports of heart failure in some patients when taking Pregabalin Sandoz; these patients were mostly elderly with cardiovascular conditions. **Before taking this medicine you should tell your doctor if you have a history of heart disease.**

- There have been reports of kidney failure in some patients when taking Pregabalin Sandoz. If while taking Pregabalin Sandoz you notice decreased urination, you should tell your doctor as stopping the medicine may improve this.

- A small number of people being treated with anti-epileptics such as Pregabalin Sandoz have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.

- When Pregabalin Sandoz is taken with other medicines that may cause constipation (such as some types of pain medications) it is possible that gastrointestinal problems may occur (e.g., constipation, blocked or paralysed bowel). Tell your doctor if you experience constipation, especially if you are prone to this problem.

- Before taking this medicine you should tell your doctor if you have a history of alcoholism or any drug abuse or dependence. Do not take more medicine than prescribed.

- There have been reports of convulsions when taking Pregabalin Sandoz or shortly after stopping Pregabalin Sandoz. If you experience a convulsion, contact your doctor immediately.

- There have been reports of reduction in brain function (encephalopathy) in some patients taking Pregabalin Sandoz when they have other conditions. Tell your doctor if you have a history of any serious medical conditions, including liver or kidney disease.

Children and adolescents
The safety and efficacy in children and adolescents (under 18 years of age) has not been established and therefore, pregabalin should not be used in this age group.

**Other medicines and Pregabalin Sandoz**
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregabalin Sandoz and certain other medicines may influence each other (interaction). When taken with certain other medicines, Pregabalin Sandoz may potentiate the side effects seen with these medicines, including respiratory failure and coma. The degree of dizziness, sleepiness and decreased concentration may be increased if Pregabalin Sandoz is taken together with medicinal products containing:

- Oxycodone – (used as a pain-killer)
- Lorazepam – (used for treating anxiety)
- Alcohol

Pregabalin Sandoz may be taken with oral contraceptives.

**Pregabalin Sandoz with food, drink and alcohol**
Pregabalin Sandoz capsules may be taken with or without food.

It is advised not to drink alcohol while taking Pregabalin Sandoz.

**Pregnancy and breast-feeding**
Pregabalin Sandoz should not be taken during pregnancy or when breast-feeding, unless you are told otherwise by your doctor. Effective contraception must be used by women of child-bearing potential. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

**Driving and using machines**
Pregabalin Sandoz may produce dizziness, sleepiness and decreased concentration. You should not drive, operate complex machinery or engage in other potentially hazardous activities until you know whether this medicine affects your ability to perform these activities.

3. **How to take Pregabalin Sandoz**

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Your doctor will determine what dose is appropriate for you.

Pregabalin Sandoz is for oral use only.

**Peripheral and central neuropathic pain, epilepsy or Generalised Anxiety Disorder:**
- Take the number of capsules as instructed by your doctor.
- The dose, which has been adjusted for you and your condition, will generally be between 150 mg and 600 mg each day.

Your doctor will tell you to take Pregabalin Sandoz either twice or three times a day. For twice a day take Pregabalin Sandoz once in the morning and once in the evening, at about the same time each day. For three times a day take Pregabalin Sandoz once in the morning, once in the afternoon and once in the evening, at about the same time each day.

If you have the impression that the effect of Pregabalin Sandoz is too strong or too weak, talk to your doctor or pharmacist.

If you are an elderly patient (over 65 years of age), you should take Pregabalin Sandoz normally except if you have problems with your kidneys.
Your doctor may prescribe a different dosing schedule and/or dose if you have problems with your kidneys.

Swallow the capsule whole with water.

Continue taking Pregabalin Sandoz until your doctor tells you to stop.

**If you take more Pregabalin Sandoz than you should**
Call your doctor or go to the nearest hospital emergency unit immediately. Take your box or bottle of Pregabalin Sandoz capsules with you. You may feel sleepy, confused, agitated, or restless as a result of taking more Pregabalin Sandoz than you should.

**If you forget to take Pregabalin Sandoz**
It is important to take your Pregabalin Sandoz capsules regularly at the same time each day. If you forget to take a dose, take it as soon as you remember unless it is time for your next dose. In that case, just carry on with the next dose as normal. Do not take a double dose to make up for a forgotten dose.

**If you stop taking Pregabalin Sandoz**
Do not stop taking Pregabalin Sandoz unless your doctor tells you to. If your treatment is stopped it should be done gradually over a minimum of 1 week.

After stopping long and short-term Pregabalin Sandoz treatment, you need to know that you may experience certain side effects. These include, trouble sleeping, headache, nausea, feeling anxious, diarrhoea, flu-like symptoms, convulsions, nervousness, depression, pain, sweating, and dizziness. These symptoms may occur more commonly or severely if you have been taking Pregabalin Sandoz for a longer period of time.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. **Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Very common may affect more than 1 in 10 people**

- Dizziness, drowsiness, headache

**Common may affect up to 1 in 10 people**

- Increased appetite.
- Feeling of elation, confusion, disorientation, decrease in sexual interest, irritability.
- Disturbance in attention, clumsiness, memory impairment, loss of memory, tremor, difficulty with speaking, tingling feeling, numbness, sedation, lethargy, insomnia, fatigue, feeling abnormal.
- Blurred vision, double vision.
- Vertigo, problems with balance, fall.
- Dry mouth, constipation, vomiting, flatulence, diarrhoea, nausea, swollen abdomen.
- Difficulties with erection.
- Swelling of the body including extremities.
- Feeling drunk, abnormal style of walking.
- Weight gain.
- Muscle cramp, joint pain, back pain, pain in limb.
- Sore throat.

**Uncommon may affect up to 1 in 100 people**
Loss of appetite, weight loss, low blood sugar, high blood sugar.

Change in perception of self, restlessness, depression, agitation, mood swings, difficulty finding words, hallucinations, abnormal dreams, panic attack, apathy, aggression, elevated mood, mental impairment, difficulty with thinking, increase in sexual interest, problems with sexual functioning including inability to achieve a sexual climax, delayed ejaculation.

Changes in eyesight, unusual eye movement, changes in vision including tunnel vision, flashes of light, jerky movements, reduced reflexes, increased activity, dizziness on standing, sensitive skin, loss of taste, burning sensation, tremor on movement, decreased consciousness, loss of consciousness, fainting, increased sensitivity to noise, feeling unwell.

Dry eyes, eye swelling, eye pain, weak eyes, watery eyes, eye irritation.

Heart rhythm disturbances, increased heart rate, low blood pressure, high blood pressure, changes in heart beat, heart failure.

Flushing, hot flushes.

Difficulty breathing, dry nose, nasal congestion.

Increased saliva production, heartburn, numb around mouth.

Sweating, rash, chills, fever.

Muscle twitching, joint swelling, muscle stiffness, pain including muscle pain, neck pain.

Breast pain.

Difficulty with or painful urination, incontinence.

Weakness, thirst, chest tightness.

Changes in blood and liver test results (blood creatinine phosphokinase increased, alanine amino transferase increased, aspartate aminotransferase increased, platelet count decreased, neutropaenia, increase in blood creatinine, decrease in blood potassium).

Hypersensitivity, swollen face, itchiness, hives, runny nose, nose bleed, cough, snoring.

Painful menstrual periods.

Coldness of hands and feet.

**Rare may affect up to 1 in 1,000 people**

Abnormal sense of smell, swinging vision, altered perception of depth, visual brightness, vision loss.

Dilated pupils, cross eyes.

Cold sweat, tightness of the throat, swollen tongue.

Inflammation of the pancreas.

Difficulty in swallowing.

Slow or reduced movement of the body.

Difficulty with writing properly.

Increased fluid in the abdomen.

Fluid in the lungs.

Convulsions.

Changes in the recording of electrical changes (ECG) in the heart which correspond to heart rhythm disturbances.

Muscle damage.

Breast discharge, abnormal breast growth, breast growth in males.

Interrupted menstrual periods.

Kidney failure, reduced urine volume, urinary retention.

Decrease in white blood cell count.

Inappropriate behaviour.

Allergic reactions (which may include difficulty breathing, inflammation of the eyes (keratitis) and a serious skin reaction characterized by rash, blisters, peeling skin and pain).

If you experience swollen face or tongue or if your skin turns red and starts to blister or peel you should seek immediate medical advice.
Certain side effects may be more common, such as sleepiness, because patients with spinal cord injury may be taking other medicines to treat, for example, pain or spasticity, that have similar side effects to Pregabalin and the severity of these effects may be increased when taken together.

**Reporting of side effects**
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. **How to store Pregabalin Sandoz**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister, container or carton. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

**HDPE bottles:** Use within 6 months after first opening.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. **Contents of the pack and other information**

**What Pregabalin Sandoz contains**
- The active substance is pregabalin. Each hard capsule contains either 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg or 300 mg pregabalin.
- The other ingredients are pregelatinised maize starch, maize starch, talc, gelatin, titanium dioxide (E171), yellow iron oxide (E172) (all strengths except 150 mg), red iron oxide (E172) (all strengths except 50 mg and 150 mg), black iron oxide (E172) (only 25 mg and 300 mg).

**What Pregabalin Sandoz looks like and contents of the pack**

<table>
<thead>
<tr>
<th>Capsule Strength</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 mg capsules</td>
<td>Pale yellow-brown opaque cap and body, capsule size 4 (14.3 mm x 5.3 mm) filled with white to nearly white coloured powder.</td>
</tr>
<tr>
<td>50 mg capsules</td>
<td>Light yellow opaque cap and body, capsule size 3 (15.9 mm x 5.8 mm) filled with white to nearly white coloured powder.</td>
</tr>
<tr>
<td>75 mg capsules</td>
<td>Red opaque cap and white opaque body, capsule size 4 (14.3 mm x 5.3 mm) filled with white to nearly white coloured powder.</td>
</tr>
<tr>
<td>100 mg capsules</td>
<td>Red opaque cap and body, capsule size 3 (15.9 mm x 5.8 mm) filled with white to nearly white coloured powder.</td>
</tr>
<tr>
<td>150 mg capsules</td>
<td>White opaque cap and body, capsule size 2 (18.0 mm x 6.4 mm) filled with white to nearly white coloured powder.</td>
</tr>
<tr>
<td>200 mg capsules</td>
<td>Pale orange opaque cap and body, capsule size 1 (19.4 mm x 6.9 mm) filled with white to nearly white coloured powder.</td>
</tr>
<tr>
<td>225 mg capsules</td>
<td>Pale orange opaque cap and white opaque body, capsule size 1 (19.4 mm x 6.9 mm) filled with white to nearly white coloured powder.</td>
</tr>
<tr>
<td>300 mg capsules</td>
<td>Red opaque cap and pale yellow-brown opaque body, capsule size 0 (21.7 mm x 7.6 mm) filled with white to nearly white coloured powder.</td>
</tr>
</tbody>
</table>

Pregabalin Sandoz is available in the following presentations:
PVC/PVDC//Alu blisters packed in carton.
PVC/PVDC//Alu unit dose blisters packed in carton.
HDPE container with PP screw cap packed in carton.

25 mg capsules:
Blisters containing 14, 28, 56, 70, 84, 100 or 120 hard capsules.
Unit dose blisters containing 56 x 1, 84 x 1 or 100 x 1 hard capsules.
HDPE bottles containing 200 hard capsules.

50 mg capsules:
Blisters containing 14, 21, 28, 56, 84 or 100 hard capsules.
Unit dose blisters containing 84 x 1 hard capsules.
HDPE bottles containing 200 hard capsules.

75 mg capsules:
Blisters containing 14, 21, 28, 56, 70, 84, 100 or 120 hard capsules.
Unit dose blisters containing 14, 56, 84, 100 or 210 (3 x 70) hard capsules.
HDPE bottles containing 100, 200 or 250 hard capsules.

100 mg capsules:
Blisters containing 14, 21, 28, 56, 84 or 100 hard capsules.
Unit dose blisters containing 84 or 100 hard capsules.

150 mg capsules:
Blisters containing 14, 21, 28, 56, 70, 84, 100 or 120 hard capsules.
Unit dose blisters containing 56, 84, 100 or 210 (3 x 70) hard capsules.
HDPE bottles containing 100, 200 or 250 hard capsules.

200 mg capsules:
Blisters containing 21, 28, 84 or 100 hard capsules.
Unit dose blisters containing 84 or 100 hard capsules.

225 mg capsules:
Blisters containing 14, 56, 70, 84, 100 or 120 hard capsules.

300 mg capsules:
Blisters containing 14, 21, 28, 56, 70, 84 (2 x 42), 100 (2 x 50) or 120 (2 x 60) hard capsules.
Unit dose blisters containing 56, 84 (2 x 42), 100 (2 x 50) or 210 (3 x 70) hard capsules.
HDPE bottles containing 100, 200 or 250 hard capsules.

Not all pack sizes may be marketed

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**Manufacturer**
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Detailed information on this medicine is available on the European Medicines Agency web site: