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INSTRUCTION
for medical use
ZONIK®

Composition:
active substance: pregabalin;
each hard capsule contains 25 mg or 50 mg of pregabalin;
excipients: pregelatinised starch, magnesium stearate, hard gelatin capsule (gelatin, purified water, titanium dioxide (E 171), sodium lauryl sulfate).

Pharmaceutical form. Hard capsules.
Main physical and chemical properties:
hard capsule 25 mg: hard gelatin size '4' capsule, with white body and cap containing white to off white powder;
hard capsule 50 mg: hard gelatin size '4' capsule, with white body and cap containing white to off white powder.

Pharmacotherapeutic group. Antiepileptics. Other antiepileptics. Pregabalin. ATC code: N03A X16.

Pharmacological properties.
Pharmacodynamics.
The active substance of Zonik®, 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 (CNS).
Clinical efficacy and safety.
– *Neuropathic pain.*
Efficacy has been shown in diabetic neuropathy, post herpetic neuralgia and spinal cord injury. Efficacy has not been studied in other models of neuropathic pain.
The safety and efficacy profiles of treatment with pregabalin of up to 13 weeks with twice a day dosing (BID) and up to 8 weeks with three times a day (TID) dosing were similar.
During the treatment with pregabalin 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.
– *Epilepsy.*

Adjunctive treatment. The safety and efficacy profiles of 12-week administration duration for BID and TID dosing regimens were similar. A reduction in seizure frequency was observed during the first week.
Children. 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 reactions observed in patients from 3 months to 16 years of age with partial onset seizures were similar to those observed in adults. Adverse reactions of pyrexia and upper respiratory infections were observed more frequently in epilepsy patients from 3 months to 16 years of age than in adults (see "Administration and dosage", "Adverse reactions" and "Pharmacokinetics" sections).
Monotherapy (newly diagnosed patients). Pregabalin and lamotrigine were similarly safe and well tolerated.
– *Generalised anxiety disorder.*
Relief of the symptoms of generalised anxiety disorder as reflected by the Hamilton Anxiety Rating Scale (HAM-A) was observed during the first week of treatment.
– *Fibromyalgia.*
The studies showed a reduction in pain by visual analog scale. In addition, improvement was demonstrated based on a patient global assessment, and on the Fibromyalgia Impact Questionnaire.
Children. The most frequently observed adverse reactions in the clinical trial included dizziness, nausea, headache, weight increased, and fatigue. The overall safety profile in adolescents was similar to that observed in adults with fibromyalgia.
Pharmacokinetics.
Pregabalin steady-state pharmacokinetics are similar in healthy volunteers, patients with epilepsy taking 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.
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.
Metabolism.
Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabeled 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 "Pharmacokinetics" section. Renal impairment).
Dose adjustment in patients with reduced renal function or undergoing haemodialysis is necessary (see "Administration and dosage" section, 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 "Administration and dosage" section, 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.

Children.

Pregabalin pharmacokinetics were evaluated in paediatric patients with epilepsy. 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 area under the plasma drug concentration-time curve (AUC) parameters increased in a linear manner with increasing dose. 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.

It was established 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 "Children", "Adverse reactions" and "Pharmacodynamics" sections).

Elderly patients.

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 "Administration and dosage" section, Table 1).

Breast-feeding.

Lactation had little to no influence on pregabalin pharmacokinetics when taking 150 mg pregabalin every 12 hours (300 mg daily dose). 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 is 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.

Clinical characteristics.

Indications.

Neuropathic pain.
Zonik® is indicated for the treatment of peripheral and central neuropathic pain in adults.
Epilepsy.
Zonik® is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.
Generalised anxiety disorder.
Zonik® is indicated for the treatment of generalised anxiety disorder in adults.
Fibromyalgia.

Contraindications.
Hypersensitivity to the active substance or to any of the excipients listed in "Composition" section.

Interaction with other medicinal products and other forms of interactions.
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 ethinyloestradiol.
Co-administration of pregabalin with the oral contraceptives norethisterone and/or ethinyloestradiol does not influence the steady-state pharmacokinetics of either substance.
CNS influencing medical products.
Pregabalin may potentiate the effects of ethanol and lorazepam. There are reports of respiratory failure, coma and deaths in patients taking pregabalin and opioids and/or other CNS depressant medicinal products. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone.

Interactions in elderly patients.
No specific pharmacodynamic interaction studies were conducted in elderly volunteers. Interaction studies have only been performed in adults.

Special precautions.
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 of hypersensitivity reactions, including cases of angioedema. Pregabalin should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper airway swelling occur.
Severe cutaneous adverse reactions.
Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported rarely in association with pregabalin treatment. At the time of Zonik® prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms

suggestive of these reactions appear, pregabalin should be withdrawn immediately and an alternative treatment considered (as appropriate).

Dizziness, somnolence, loss of consciousness, confusion, and mental impairment.

Pregabalin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in the elderly population. There have also been 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 "Pharmacodynamics" section).

Visual adverse reactions have also been reported, including loss of vision, visual blurring, or other changes of visual acuity, many of which were transient. Discontinuation of pregabalin may result in resolution or improvement of these visual symptoms.

Renal failure.

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

Withdrawal of concomitant anti-epileptic medicinal products.

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

Congestive heart failure.

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

Treatment of central neuropathic pain due to spinal cord injury.

In the treatment of central neuropathic pain due to spinal cord injury the incidence of adverse reactions in general, central nervous system adverse reactions and especially somnolence was increased. This may be attributed to an additive effect due to concomitant medicinal products (e.g. anti-spasticity agents) needed for this condition. This should be considered when prescribing pregabalin in this condition.

Respiratory depression.

There have been reports of severe respiratory depression in relation to pregabalin use. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment, concomitant use of CNS depressants and the elderly may be at higher risk of experiencing this severe adverse reaction. Dose adjustments may be necessary in these patients (see "Administration and dosage" section).

Suicidal risk.

Suicidal ideation/behaviour/actions have been reported in patients treated with anti-epileptic agents (including pregabalin) in several indications (see "Adverse reactions" section). A meta-analysis of randomised placebo-controlled studies of anti-epileptic drugs has also shown a small increased suicidal risk. The mechanism of this risk is not known. In the post-marketing period, cases of suicidal ideation/behavior have been observed in patients treated with pregabalin (see "Adverse reactions"). An epidemiologic study using a self-controlled study design (comparing

treatment periods with no treatment periods in an individual) demonstrated an increased risk of new suicidal behavior and death by suicide in patients receiving pregabalin.
Therefore, patients should be monitored for signs of suicidal ideation/behaviour/actions, and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should these signs emerge. Discontinuation of pregabalin treatment should be considered in case of suicidal ideation/behavior.
Reduced lower gastrointestinal tract function.
There are postmarketing reports of events related to reduced lower gastrointestinal tract function (e.g. intestinal obstruction, paralytic ileus, constipation) when pregabalin was co-administered with medications that have the potential to produce constipation, such as opioid analgesics. When pregabalin and opioids will be used in combination, measures to prevent constipation may be considered (especially in female patients and elderly).
Concomitant use with opioids.
Caution is advised when prescribing pregabalin concomitantly with opioids due to risk of CNS depression (see "Interaction with other medicinal products and other forms of interactions" section). In a case-control study, those patients who took pregabalin concomitantly with an opioid had an increased risk for opioid-related death compared to opioid use alone (adjusted odds ratio [aOR], 1.68 [95% CI, 1.19–2.36]). This increased risk was observed at low doses of pregabalin (≤ 300 mg, aOR 1.52 [95% CI, 1.04–2.22]) and there was a trend for a greater risk at high doses of pregabalin (> 300 mg, aOR 2.51 [95% CI 1.24–5.06]).
Misuse, abuse potential or dependence.
Pregabalin can cause drug dependence, which can occur at therapeutic doses. Cases of misuse, abuse and dependence have been reported. Patients with a history of substance abuse may be at a higher risk of misuse, abuse, and dependence with pregabalin and should be used with caution. Before prescribing pregabalin, the risk of misuse, abuse or dependence should be carefully assessed.
Patients treated with pregabalin should be monitored for symptoms of misuse, abuse, or dependence, such as the development of tolerance, dose escalation, and drug-seeking behavior.
Withdrawal symptoms.
Withdrawal symptoms have been observed after discontinuing short-term or long-term pregabalin therapy. The following symptoms have been reported: insomnia, headache, nausea, anxiety, diarrhea, flu-like syndrome, nervousness, depression, pain, convulsions, hyperhidrosis, and dizziness. Withdrawal symptoms after discontinuing pregabalin may indicate drug dependence (see section "Adverse reactions"). This information should be communicated to the patient before starting therapy. If pregabalin must be withdrawn, it is recommended to do so gradually over at least 1 week regardless of the indications (see section "Administration and dosage").
Seizures, including status epilepticus and grand mal seizures, may occur during or shortly after pregabalin therapy.
Data on pregabalin withdrawal after long-term use indicate that the frequency and severity of withdrawal symptoms may be dose-dependent.
Encephalopathy.
Cases of encephalopathy have been reported, mostly in patients with underlying conditions that may precipitate encephalopathy.
Women of childbearing potential / contraception.
Pregabalin use in the first-trimester of pregnancy may cause major congenital malformations in the unborn child. Zonik® should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus. Women of childbearing potential have to use effective contraception during treatment (see "Use in pregnancy and lactation" section).
Excipients.

This medicine contains less than 1 mmol sodium per capsule, that is to say essentially 'sodium-free'.

Use in pregnancy and lactation.
Women of childbearing potential / contraception.
Women of childbearing potential have to use effective contraception.
Pregnancy.
Studies in animals have shown reproductive toxicity. Pregabalin has been shown to cross the placenta in rats. Pregabalin may cross the human placenta.
Major congenital malformations (MCM)
Data from a Nordic observational study of more than 2700 pregnancies exposed to pregabalin in the first trimester showed a higher prevalence of major congenital malformations (MCM) among the paediatric population (live or stillborn) exposed to pregabalin compared to the unexposed population (5.9% vs. 4.1%).
The risk of MCM among the paediatric population exposed to pregabalin in the first trimester was slightly higher compared to unexposed population (adjusted prevalence ratio and 95% confidence interval: 1.14 (0.96–1.35)), and compared to population exposed to lamotrigine (1.29 (1.01–1.65)) or to duloxetine (1.39 (1.07–1.82)).
The analyses on specific MCM showed higher risks for orofacial clefts and malformations of the eye, the nervous system, urinary malformations and genital malformations, but numbers were small and estimates imprecise.
Zonik® 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.

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

Administration and dosage.
Administration.
Zonik® can be taken with or without food.
This drug is for oral use only.
Dosage.
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 the first week of treatment. The maximum dose of 600 mg per day may be achieved after one more 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.
Fibromyalgia.
The recommended dose for the treatment of fibromyalgia is from 300 to 450 mg per day. The treatment should be started with a dose 75 mg twice a day (150 mg once a day). Based on efficacy and tolerability, the dose may be increased to 150 mg twice a day (300 mg a day) after 1 week. For the patients for which the treatment with a dose of 300 mg a day in not efficient enough, the dose can be increased to 225 mg twice a day (450 mg a day). Although there are studies of treatment with a dose of 600 mg per day, there is no evidence that this dose will be an additional advantage; this dose has been also less tolerable. Taking into account dose-dependent adverse reactions, administration of doses more than 450 mg per day is not recommended. Since pregabalin is primarily eliminated by renal excretion, the dosage of the drug should be adjusted for patients with renal function impairment.
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 "Special precautions" and "Adverse reactions" sections).
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 "Pharmacokinetics" section), 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:

$$CLcr(\text{ml/min}) = \left[\frac{1{,}23 \times [140 - \text{age (years)}] \times \text{weight (kg)}}{\text{serum creatinine } (\mu\text{mol/l})}\right] (\times\, 0.85 \text{ for female patients})$$

Pregabalin is removed effectively from plasma by haemodialysis (50% of drug in 4 hours). For patients receiving haemodialysis, the pregabalin daily dose should be adjusted based on renal function. In addition to the daily dose, a supplementary dose should be given immediately following every 4-hour haemodialysis treatment (see Table 1).

Table 1. Pregabalin dose adjustment based on renal function.

Creatinine clearance (CLcr) (ml/min)	*Total pregabalin daily dose**		*Dose regimen*
	Starting dose (mg/day)	*Maximum dose (mg/day)*	
≥ 60	150*	600	BID or TID
≥ 30–< 60	75*	300*	BID or TID
≥ 15–<30	25–50*	150*	Once daily or BID
< 15	25*	75*	Once daily
Supplementary dosage following haemodialysis (mg)			
	25*	100*	Single dose+

** Total daily dose (mg/day) should be divided into some doses according to dosage regimen to get the dose for single administration (mg/dose).*

+ Supplementary dose is a single additional dose.

Hepatic impairment.

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

Elderly patients.

Elderly patients may require a dose reduction of pregabalin due to a decreased renal function (see "Pharmacokinetics" section).

Children.

Safety and efficacy of pregabalin when used by children under the age of 18 years have not been established. Currently available information is provided in the "Adverse reactions" section, and in "Pharmacodynamics" and "Pharmacokinetics" sections, however, based on them, it is impossible to provide any recommendations on the dosage to this category of patients.

Overdose.

The most commonly reported adverse reactions observed when pregabalin was taken in overdose included somnolence, confusional state, agitation, and restlessness. Also the cases of seizures have been reported.

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 "Administration and dosage" section, Table 1).

Adverse reactions.

In clinical trials, the most commonly reported adverse reactions were dizziness and somnolence. Adverse reactions were usually mild to moderate in intensity.

All adverse reactions, which occurred at an incidence greater than placebo and in more than one patient, are listed below 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 "Special precautions" section).

Infections and infestations.

Common: nasopharyngitis.

Blood and lymphatic system disorders.
Uncommon: neutropaenia.
Immune system disorders.
Uncommon: hypersensitivity.
Rare: angioedema, allergic reaction, anaphylactoid reactions.
Metabolism and nutrition disorders.
Common: appetite increased.
Uncommon: anorexia, hypoglycaemia.
Psychiatric disorders.
Common: euphoric mood, confusion, irritability, disorientation, insomnia, libido decreased.
Uncommon: hallucination, panic attack, restlessness, agitation, depression, depressed mood, elevated mood, aggression, mood swings, depersonalisation, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy.
Rare: disinhibition, suicidal ideation/behaviour (see "Special precautions" section).
Not known: drug dependence.
Nervous system disorders.
Very common: dizziness, somnolence, headache.
Common: ataxia, coordination abnormal, tremor, dysarthria, amnesia, memory impairment, disturbance in attention, paraesthesia, hypoaesthesia, sedation, balance disorder, lethargy.
Uncommon: syncope, stupor, myoclonus, loss of consciousness, psychomotor hyperactivity, dyskinesia, dizziness postural, intention tremor, nystagmus, cognitive disorder, mental impairment, speech disorder, hyporeflexia, hyperaesthesia, burning sensation, ageusia, malaise, apathy, periarticular paresthesia, myoclonus.
Rare: convulsions, parosmia, hypokinesia, dysgraphia, parkinsonism, gipalgesia, dependence, cerebellar syndrome, cogwheel sign, coma, delirium, encephalopathy, extrapyramidal syndrome, Guinea-Barré syndrome, intracranial hypertension, manic reactions, paranoid reactions, sleep disorders.
Eye disorders.
Common: vision blurred, diplopia, conjunctivitis.
Uncommon: peripheral vision loss, visual disturbance, eye swelling, visual field defect, visual acuity reduced, eye pain, asthenopia, photopsia, dry eye, lacrimation increased, eye irritation, blepharitis, disturbance of accommodation, eye bleeding, photophobia, albedo retinae.
Rare: vision loss, keratitis, oscillopsia, altered visual depth perception, mydriasis, strabismus, visual brightness, anisocoria, corneal ulcer, exophthalmos, paralysis of the ocular muscle, iritis, keratoconjunctivitis, myositis, nocturnal blindness, ophthalmoplegia, optic nerve atrophy, swelling of the optic disc, ptosis, uveitis.
Ear and labyrinth disorders.
Common: vertigo.
Uncommon: hyperacusis.
Cardiac disorders.
Uncommon: tachycardia, atrioventricular block first degree, sinus bradycardia, congestive heart failure.
Rare: QT prolongation, sinus tachycardia, sinus arrhythmia.
Vascular disorders.
Uncommon: hypotension, hypertension, hot flushes, flushing, peripheral coldness.
Respiratory, thoracic and mediastinal disorders.
Common: pharyngolaryngeal pain.
Uncommon: dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness.
Rare: pulmonary oedema, throat tightness, laryngospasm, apnea, atelectasis, bronchiolitis, hiccup, lung fibrosis, yawning.
Not known: respiratory depression.

Gastrointestinal disorders.
Common: vomiting, nausea, constipation, diarrhoea, flatulence, abdominal distension, dry mouth, gastroenteritis.
Uncommon: gastrooesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral, cholecystitis, cholelithiasis, colitis, gastrointestinal bleeding, melena, tongue edema, rectal bleeding.
Rare: ascites, pancreatitis, swollen tongue, dysphagia, aphthous stomatitis, ulcer of the esophagus, periodontal abscess.
Hepatobiliary system disorders.
Uncommon: increased levels of liver enzymes*.
Uncommon: jaundice.
Very rare: liver failure, hepatitis.
Skin and subcutaneous tissue disorders.
Common: decubitus.
Uncommon: rash papular, urticaria, hyperhidrosis, itching, alopecia, dry skin, eczema, hirsutism, skin ulcers, vesiculobullous rash.
Rare: Stevens Johnson syndrome, toxic epidermal necrolysis, cold sweat, exfoliative dermatitis, lichenoid dermatitis, melanosis, nail disorders, petechiae rash, purpura, pustular rash, skin atrophy, skin necrosis, skin and subcutaneous nodules.
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, albuminuria, hematuria, kidney stones, nephritis.
Rare: renal failure, oliguria, urinary retention, acute renal failure, glomerulonephritis, pyelonephritis.
Reproductive system and breast disorders.
Common: erectile dysfunction, impotence.
Uncommon: sexual dysfunction, ejaculation delayed, dysmenorrhoea, breast pain, leucorrhoea, menorrhagia, metroragia.
Rare: amenorrhoea, breast discharge, breast enlargement, gynaecomastia, cervicitis, balanitis, epididymitis.
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 fever, thirst, chills, general weakness, malaise, abscess, pimelitis, photosensitivity reaction.
Rare: granuloma, intentional damage, retroperitoneal fibrosis, shock.
Investigations.
Common: weight increased.
Uncommon: blood creatine phosphokinase increased, blood glucose increased, platelet count decreased, blood creatinine increased, blood potassium decreased, weight decreased.
Rare: white blood cell count decreased.
* Alanine aminotransferase increased (ALT) and aspartate aminotransferase increased (AST).

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

Concerning discontinuation of long-term treatment of pregabalin, data suggest that the incidence and severity of withdrawal symptoms may be dose-related (see sections “Administration and dosage” and “Special precautions”).
Children. The pregabalin safety profile observed in paediatric studies was similar to that observed in the adult studies of patients with epilepsy. The most common adverse events observed in the were somnolence, pyrexia, upper respiratory tract infection, increased appetite, weight increased, and nasopharyngitis.
Reporting of suspected adverse reactions.
The reporting of adverse reactions after the registration of the medicinal product is of great importance. This makes it possible to monitor the benefit/risk ratio when using this medicinal product. Medical and pharmaceutical workers, as well as patients or their legal representatives should be notified of all cases of suspected adverse reactions and lack of efficacy of the medicinal product through the Automated Pharmacovigilance Information System at the link: https://aisf.dec.gov.ua.

Shelf-life.
2 years.

Storage conditions.
Store at a temperature not more than 25°C in the original package.
Keep out of reach of children.

Package.
14 capsules in a blister. 2 or 4 blisters in a carton package.

Conditions of supply.
By prescription.

Manufacturer.
KUSUM HEALTHCARE PVT LTD.

Location of manufacturer and its address of business activity.
SP-289 (A), RIICO Industrial area, Chopanki, Bhiwadi, Dist. Alwar (Rajasthan), India.

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