ZERICA Capsules

(P r e g a b a l i n)

زریکا کیپسول

(پریگابالین)

DESCRIPTION:
Pregabalin is described chemically as (S)-3-(aminomethyl)-5-methylhexanoic acid. The molecular formula is $C_8H_{17}NO_2$ and the molecular weight is 159.23.

COMPOSITION:
Zerica 50mg Capsule
Each capsule contains :
Pregabalin U.S.P. 50mg
(Product Specs.: Bosch)

Zerica 75mg Capsule
Each capsule contains :
Pregabalin U.S.P. 75mg
(Product Specs.: Bosch)

Zerica 100mg Capsule
Each capsule contains :
Pregabalin U.S.P. 100mg
(Product Specs.: Bosch)

CLINICAL PHARMACOLOGY:
Pharmacodynamic Properties:
Pharmacotherapeutic group: Antiepileptics, other antiepileptics, ATC code: N03AX16.

Mechanism of Action:
The active substance, pregabalin, is a gamma-aminobutyric acid analogue ((S)-3-(aminomethyl)-5-methylhexanoic acid). Pregabalin binds to an auxiliary subunit (α2-δ protein) of voltage-gated calcium channels in the central nervous system.

Pharmacokinetic Properties
Absorption:
Pregabalin is rapidly absorbed when administered in the fasted state, with peak plasma concentrations occurring within 1 hour following both single and multiple dose administration. Pregabalin oral bioavailability is estimated to be ≥ 90 % and is independent of dose. Following repeated administration, steady state is achieved within 24 to 48 hours. The rate of pregabalin absorption is decreased when given with food resulting in a decrease in Cmax by approximately 25-30 % and a delay in tmax to approximately 2.5 hours. However, administration of pregabalin with food has no clinically significant effect on the extent of pregabalin absorption.

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

Metabolism:
Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabelled pregabalin, approximately 98 % of the radioactivity recovered in the urine was unchanged pregabalin. The N-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0.9 % of the dose. In preclinical studies, there was no indication of 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. Dose adjustment in patients with reduced renal function or undergoing haemodialysis is necessary.

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

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

Pediatrics:
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 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. Pregabalin pharmacokinetics in patients younger than 3 months old have not been studied.

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,

THERAPEUTIC INDICATIONS:
Neuropathic pain:
Zerica is indicated for the treatment of peripheral and central neuropathic pain in adults.

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

Generalised Anxiety Disorder:
Zerica is indicated for the treatment of Generalised Anxiety Disorder (GAD) in adults.

DOSAGE AND ADMINISTRATION:
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.

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, dose reduction in patients with compromised renal function must be individualised according to creatinine clearance. 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.

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	OD or BID
<15	25	75	OD
Supplementary dosage following hemodialysis (mg)			
	25	100	Single dose**

Patients with Hepatic Impairment:
No dose adjustment is required for patients with hepatic impairment.

Elderly:
Elderly (over 65 years of age) patients may require a dose reduction of pregabalin due to a decreased renal function.

Paediatric population:
The safety and efficacy of Zerica in children below the age of 12 years and in adolescents (12-17 years of age) have not been established.

Method of Administration:
Zerica may be taken with or without food. Zerica is for oral use only.

CONTRAINDICATIONS:
Hypersensitivity to the active substance or to any of the excipients.

WARNINGS AND PRECAUTIONS:
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 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.

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

Hypersensitivity reactions:
There have been reports in the postmarketing experience of hypersensitivity reactions, including cases of angioedema. Pregabalin should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper airway swelling occur.

Dizziness, somnolence, loss of consciousness, confusion, and mental impairment:
Pregabalin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in the elderly population. There have also been post-marketing reports of loss of consciousness, confusion and mental impairment. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medicinal product.

Vision-related effects:
higher proportion of patients treated with pregabalin reported blurred vision than did patients treated with placebo which resolved in a majority of cases with continued dosing. In the clinical studies where ophthalmologic testing was conducted, the incidence of visual acuity reduction and visual field changes was greater in pregabalin-treated patients than in placebo-treated patients; the incidence of fundoscopic changes was greater in placebo-treated patients. In the post-marketing experience, visual adverse reactions have also been reported, including loss of vision, visual blurring or other changes of visual acuity, many of which were transient. Discontinuation of pregabalin may result in resolution or improvement of these visual symptoms.

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

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

Withdrawal symptoms:
After discontinuation of short-term and long-term treatment with pregabalin withdrawal symptoms have been observed in some patients. The following events have been mentioned: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, nervousness, depression, pain, convulsion, hyperhidrosis and dizziness, 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 post-marketing reports of congestive heart failure in some patients receiving pregabalin. These reactions are mostly seen in elderly cardiovascular compromised patients during pregabalin treatment for a neuropathic indication. Pregabalin should be used with caution in these patients. Discontinuation of pregabalin may resolve the reaction.

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

Suicidal ideation and behaviour:
Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. 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).

Concomitant use with opioids:
Caution is advised when prescribing pregabalin concomitantly with opioids due to risk of CNS depression. In a case-control study of opioid users, those patients who took pregabalin concomitantly with an opioid had an increased risk for opioid-related death compared to opioid use alone.

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.

DRUG INTERACTIONS:
Since pregabalin is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans, does not inhibit drug metabolism in vitro, and is not bound to plasma proteins. No clinically relevant pharmacokinetic interactions were observed between pregabalin and phenytoin, carbamazepine, valproic acid, lamotrigine, gabapentin, lorazepam, oxycodone or ethanol. Population pharmacokinetic analysis indicated that oral antidiabetics, diuretics, insulin, phenobarbital, tiagabine and topiramate had no clinically significant effect on pregabalin clearance.

Oral contraceptives, norethisterone and/or ethinyl oestradiol:
Co-administration of pregabalin with the oral contraceptives norethisterone and/or ethinyl oestradiol does not influence the steady-state pharmacokinetics of either substance.

Central nervous system influencing medical products:
Pregabalin may potentiate the effects of ethanol and lorazepam. In the postmarketing experience, there are reports of respiratory failure, coma and deaths in patients taking pregabalin and opioids and/or other central nervous system (CNS) depressant medicinal products. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone.

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

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.

ADVERSE EFFECTS:
Very Common:
Dizziness, somnolence, headache.

Common:
Nasopharyngitis, Appetite increased, Euphoric mood, confusion, irritability, disorientation, insomnia, libido decreased, Ataxia, coordination abnormal, tremor, dysarthria, amnesia, memory impairment, disturbance in attention, paraesthesia, hypoaesthesia, sedation, balance disorder, lethargy, Vision

blurred, diplopia, Vertigo, Vomiting, nausea, constipation, diarrhoea, flatulence, abdominal distension, dry mouth, Muscle cramp, arthralgia, back pain, pain in limb, cervical spasm, Erectile dysfunction, Oedema peripheral, oedema, gait abnormal, fall, feeling drunk, feeling abnormal, fatigue, Weight increased.

Uncommon:
Neutropenia, Hypersensitivity, Anorexia, hypoglycaemia, Hallucination, panic attack, restlessness, agitation, depression, depressed mood, elevated mood, aggression, mood swings, depersonalisation, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy, 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, Peripheral vision loss, visual disturbance, eye swelling, visual field defect, visual acuity reduced, eye pain, asthenopia, photopsia, dry eye, lacrimation increased, eye irritation, Hyperacusis, Tachycardia, atrioventricular block first degree, sinus bradycardia, congestive heart failure, Hypotension, hypertension, hot flushes, flushing, peripheral coldness, Dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness, Gastrooesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral, Elevated liver enzymes, Rash papular, urticaria, hyperhidrosis, pruritus, Joint swelling, myalgia, muscle twitching, neck pain, muscle stiffness, Urinary incontinence, dysuria, Sexual dysfunction, ejaculation delayed, dysmenorrhoea, breast pain, Generalised oedema, face oedema, chest tightness, pain, pyrexia, thirst, chills, asthenia, Blood creatine phosphokinase increased, blood glucose increased, platelet count decreased, blood creatinine increased, blood potassium decreased, weight decreased.

Rare:
Angioedema, allergic reaction, Disinhibition, Convulsions, parosmia, hypokinesia, dysgraphia, Parkinsonism, Vision loss, keratitis, oscillopsia, altered visual depth perception, mydriasis, strabismus, visual brightness, QT prolongation, sinus tachycardia, sinus arrhythmia, Pulmonary oedema , throat tightness, Ascites, pancreatitis, swollen tongue, dysphagia, Jaundice, Stevens Johnson syndrome, cold sweat, Toxic Epidermal Necrolysis, Rhabdomyolysis, Renal failure, oliguria, urinary retention, Amenorrhoea, breast discharge, breast enlargement, gynaecomastia, White blood cell count decreased.

Very Rare:
Hepatic failure, hepatitis.

Not Known:
Respiratory depression.

USE IN PREGNANCY AND LACTATION:
Pregnancy:
There is a limited amount of data from the use of pregabalin in pregnant women. Zerica should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the foetus). No sudden discontinuation of antiepileptic therapy should be undertaken as this may lead to breakthrough seizures, which could have serious consequences for both mother and child.

Lactation:
Pregabalin is excreted in 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.

OVERDOSE:
In the post-marketing experience, the most commonly reported adverse reactions observed when pregabalin was taken in overdose included somnolence, confusional state, agitation, and restlessness. Seizures were also reported. In rare occasions, cases of coma have been reported. Treatment of pregabalin overdose should include general supportive measures and may include haemodialysis if necessary.

SHELF LIFE:
2 years

STORAGE:
Protect from heat, sunlight & moisture, store below (30°C).
The expiration date refer to the product correctly stored at the required condition. Keep out of the reach of children.
Patients and healthcare professionals can also report suspected adverse drug reaction at ade@bosch-pharma.com.
To be sold on prescription of a registered medical practitioner only.

PRESENTATION:
ZERICA 50mg capsules are available in Alu Alu pack of 3x10's.
ZERICA 75mg capsules are available in Alu Alu pack of 14s.
ZERICA 100mg capsules are available in Alu Alu pack of 14s.

ہدایات :

دھوپ، گرمی اور نمی سے محفوظ ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
بچوں کی پہنچ سے دُور رکھیں۔
صرف مستند ڈاکٹر کے نسخے پر فروخت کے لئے۔

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ISO 9001:2015 Certified Company