Zega®

Composition

Each hard capsule of Zega® contains 75,150 or 300 mg of pregabalin.
List of excipients
Mannitol, Povidone K30, Croscarmellose sodium, Microcrystalline cellulose, Magnesium stearate.

Properties

Zega® (Pregabalin) is a gamma-aminobutyric acid analogue. Its oral bioavailability is ≥ 90% that is independent of dose. Administration of Pregabalin with food has no clinically significant effect on the extent of its absorption. Pregabalin is widely distributed into different body tissues and is not bound to plasma proteins. It undergoes negligible metabolism in humans and almost 98% of the dose recovered in urine as unchanged drug.

Therapeutic indications

Neuropathic pain
Zega® is indicated for the treatment of peripheral neuropathic pain in adults.

Epilepsy
Zega® is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalization.

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

Dosage and method of administration
The dose range is 150 to 600 mg per day given in either two or three divided doses.
Zega® may be taken with or without food.

Neuropathic pain
Zega® treatment can be started at a dose of 150 per day. Based on individual patient response and tolerability, the dosage may be increased to 300 mg per day after an interval of 3 to 7 days, and if needed, to a maximum dose of 600 mg per day after an additional 7- day interval.

Epilepsy
Zega® treatment can be started with a dose of 150 mg per day. Based on individual patient response and tolerability, the dosage may be increased to 300 mg per day after 1 week. The maximum dosage of 600 mg per day may be achieved after an additional week.

Generalized Anxiety Disorder
The dose range of Zega® is 150 to 600 mg per day given as two or three divided doses. The need for treatment should be reassessed regularly.

Zega® treatment can be started with a dose of 150 mg per day. Based on individual patient response and tolerability, the dosage may be increased to 300 mg per day after 1 week. Following an additional week the dosage may be increased to 450 mg per day. The maximum dosage of 600 mg per day may be achieved after an additional week.

Discontinuation of pregabalin

In accordance with current clinical practice, if pregabalin has to be discontinued, it is recommended that 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, dosage reduction in patients with compromised renal function must be individualized according to creatinine clearance (CLcr), as indicated in table below determined using the following formula:

$$\text{CLCr (ml/min)} = \frac{[1.23 \times (140 - \text{age (years)}) \times \text{weight (kg)}]}{72 \times \text{serum creatinine (mg/dl)}} \; (\times 0.85 \text{ for female patients})$$

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

Pregabalin dosage 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	QD or BID
< 15	25	75	QD
Supplementary dosage following haemodialysis (mg)			
	25	100	Single dose +

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

Use in patients with hepatic impairment
No dosage adjustment is required for patients with hepatic impairment.
Use in children and adolescents
Pregabalin is not recommended for use in children below the age of 12 years and adolescents (12-17 years of age) due to insufficient data on safety and efficacy.
Use in the elderly (over 65 years of age)
Elderly patients may require a dose reduction of pregabalin due to a decreased renal function.

Contraindications
Hypersensitivity to the active substance or to any of the excipients.

Special warnings and special precautions for use
In accordance with current clinical practice, some diabetic patients who gain weight on pregabalin treatment may need to adjust hypoglycemic medications.
Pregabalin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in the elderly population. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medication.
There are insufficient data for the withdrawal of concomitant antiepileptic medicinal products once seizure control with

pregabalin in the add- on situation has been reached, in order to reach monotherapy on pregabalin.
After discontinuation of short-term and long-term treatment with Pregabalin, withdrawal symptoms have been observed in some patients. The following events have been mentioned: insomnia, headache, nausea, diarrhea, flu syndrome, nervousness, depression, pain, sweating and dizziness. The patient should be informed about this at the start of the treatment.
Concerning discontinuation of long-term treatment of Pregabalin, there are no data of the incidence and severity of withdrawal symptoms in relation to duration of use and dosage of Pregabalin.
In the treatment of central neuropathic pain due to spinal cord injury, the incidence of adverse events in general, CNS adverse events and especially somnolence was increased. This may be attributed to an additive effect due to concomitant medication (e.g. anti-spasticity agents) needed for this condition. This should be considered when prescribing Pregabalin in this condition.

Drug Interactions
Since pregabalin is predominantly excreted unchanged in the urine, undergoes negligible metabolism is humans (< 2% of 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.

Accordingly, in in-vivo studies no clinically relevant pharmacokinetic interactions were observed between pregabalin and phenytoin, carbamazepine, valproic acid, lamotrigine, gabapetin, lorazepam, oxycodone or ethanol. Population pharmacokinetic analysis indicated that oral antidiabetics, diuretics, insulin, phenobarbital, tiagabine and topiramate had no clinically significant effects on pregabalin clearance.
Co-administration of pregabalin with the oral contraceptives norethisterone and /or ethinyl oestradiol does not influence the steady-state pharmacokinetics of either substance.
Multiple oral doses of pregabalin co-administered with oxycodone, lorazepam, or ethanol did not result in clinically important effects on respiration. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone. Pregabalin may poentiate the effects of ethanol and lorazepam.
No specific pharmacodynamic interaction studies were conducted in elderly volunteers. Interaction studies have only been performed in adults.

Pregnancy and lactation
There are no adequate data on the use of pregabalin in pregnant women.
Studies in animals have shown reproductive toxicity. The potential risk to humans is unknown. Therefore, pregabalin should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the fetus.

Effective contraception must be used in women of child bearing potential.
It is not known if pregabalin is excreted in the breast milk of humans; however, it is present in the milk of rats. Therefore, breast – feeding is not recommended during treatment with pregabalin.

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

Undesirable effects
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 13% for patients receiving pregabalin and 7% for patients receiving placebo. The most common adverse reactions resulting in discontinuation from pregabalin treatment groups were dizziness and somnolence.
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, < 1/10), uncommon (>1/1000, <1/100) and rare (<1/1000)).

The adverse reactions listed may also be associated with the underlying diseases and / or concomitant medications.
In the treatment of central neuropathic pain due to spinal cord injury the incidence of adverse event in general, CNS adverse events and especially somnolence was increased.

Body system and Adverse drug reactions
Blood and lymphatic system disorders
Rare :Neutropenia
Metabolism and nutrition disorders
Common: Appetite increased
Uncommon: Anorexia
Rare : Hypoglycemia
Psychiatric disorders
Common : Euphoric mood, confusion, irritability, libido decreased
Uncommon : hallucination, panic attack, restlessness, agitation, depression, depressed mood, mood swings, Depersonalisation, insomnia exacerbated, word finding difficulty, abnormal dreams, , libido increased, anorgasmia, apathy
Rare : Hypersensitivity, disinhibition, elevated mood, headache
Nervous system disorders
Very common : Dizziness, somnolence

Common : Ataxia, coordination abnormal, tremor, dysarthria, memory impairment,disturbance in attention, paraesthesia
Uncommon : syncope, stupor, myoclonus, psychomotor hyperactivity, visual field defect, ageusia, dyskinesia, dizziness postural, intention tremor, nystagmus, Cognitive disorder, speech disorder, hypoaesthesia, amnesia hyporeflexia, hyperaesthesia, burning sensation,
Rare : Hypokinesia, parosmia, dysgraphia

Eye disorders

Common : Vision blurred, diplopia
Uncommon : Visual disturbance, eye swelling, visual acuity reduced, eye pain, asthenopia, dry eye, lacrimation increased
Rare : peripheral vision loss, oscillopsia, altered visual depth perception,Photopsia, eye irritation, mydriasis, strabismus, visual brightness

Ear and labyrinth disorders

Common : Vertigo
Rare : Hyperacusis

Cardiac disorders

Uncommon : Tachycardia
Rare : Atrioventricular block first degree, sinus tachycardia, sinus bradycardia ,sinus arrhythmia

Vascular disorders

Uncommon :Flushing, hot flushes
Rare :Hypotension,hypertension, peripheral coldness

Respiratory, thoracic and mediastinal disorders

Uncommon : Dyspnoea, nasal dryness

Rare : epistaxis, throat tightness ,Nasopharyngitis, cough, nasal congestion, , rhinitis, snoring

Gastrointestinal disorders

Common : vomiting,Dry mouth, constipation, flatulence

Uncommon : Abdominal distension, gastrooesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral

Rare : Ascites, pancreatitis, dysphagia, nausea

Skin and subcutaneous tissue disorders

Uncommon : rash papular , Sweating

Rare : urticaria ,Cold sweat

Musculoskeletal and connective tissue disorders

Uncommon : Muscle twitching, joint swelling, muscle cramp, myalgia, arthralgia, back pain, pain in limb, muscle stiffness

Rare : rhabdomyolysis, Cervical spasm, neck pain,

Renal and urinary disorders

Uncommon : urinary incontinence ,Dysuria

Rare : renal failure ,Oliguria

Reproductive system and breast disorders

Common : Erectile dysfunction

Uncommon : Ejaculation delayed, sexual dysfunction

Rare : Amenorrhoea, breast discharge, breast pain, dysmenorrhoea, hypertrophy breast

General disorders and administration site conditions

Common : gait abnormal , feeling drunk, Fatigue, oedema peripheral, oedema

Uncommon : fall, chest tightness, Asthenia ,thirst

Rare : anasarca, face oedema, swollen tongue, pyrexia, rigors, Pain exacerbated.

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

Overdose
In overdoses up to 15 g, no unexpected adverse reactions were reported. Treatment of pregabalin overdose should include general supportive measures and may include haemodialysis if necessary.

Storage conditions
Store below 30°C.

Presentation
Zega® 75 : Pregabalin 75 mg/Cap (Available in packs of 14 and 50 caps).
Zega® 150 : Pregabalin 150 mg/Cap (Available in packs of 50 caps).
Zega® 300 : Pregabalin 300 mg/Cap (Available in packs of 50 caps).