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measured by semen analysis.

Undesirable effects
The pregabalin clinical programme involved over 12,000 patients who were exposed to pregabalin, of whom over 7,000 were in double-blind placebo-controlled trials. The most commonly reported adverse effects were dizziness and somnolence. Adverse effects were usually mild to moderate in intensity. In all controlled studies, the discontinuation rate due to adverse events was 14% for patients receiving pregabalin and 5% for patients receiving placebo. The most common adverse effects resulting in discontinuation from pregabalin treatment groups were dizziness, sleepiness, headache, tiredness, fluid retention, nausea, blurred vision, dry mouth, weight gain, difficulty concentrating and somnolence. dizziness, sleepiness, headache, tiredness, fluid retention, nausea, blurred vision, dry mouth, weight gain, difficulty concentrating

Overdose and Treatment
Signs and Symptoms
In overdoses up to 15g, no unexpected adverse effects were reported. In post-marketing experience, the most commonly reported adverse events observed when pregabalin was taken in overdose included affective disorder, somnolence, confusional state, depression, agitation and restlessness. Seizures were also reported.
Recommended Treatment
There is no specific antidote for pregabalin. Treatment of Pregabalin-AFT overdose should be symptomatic and supportive. Consider administration of activated charcoal in the event of a potentially toxic ingestion. Activated charcoal is most effective when administered within one hour of ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected. Haemodialysis may be useful in patients with severe toxicity or those with significant renal impairment (see Section 4.2 – Dose and method of administration, Renal Impairment). Standard haemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours). Emesis is not recommended because of the potential for CNS depression and seizures.

Effects on Ability to Drive and Use Machines
Revogab may cause dizziness and somnolence and therefore may have an influence on 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.

Dosage Forms and Packaging Available
Incompatibilities
Not applicable.

Shelf life
2 years

Special precautions for storage
Store below 30°C in a dry place, protect from light.
Keep out of the reach of children

Nature and contents of container
PET bottle 120ml.

DATE OF REVISION OF THE TEXT
N/A

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
- دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر روشنی سے بچا کر خشک جگہ پر رکھیں۔
- صرف رجسٹرڈ ڈاکٹر کے نسخے پر ہی فروخت کریں۔
- ڈھکن کو اچھی طرح بند رکھیں۔
- بچوں کی پہنچ سے دور رکھیں۔

Manufactured by:
Kaizen Pharmaceuticals (Pvt.) Ltd.
E-127-129, North Western Industrial Zone,
Bin Qasim, Karachi-75020, Pakistan.

Art No: 1002

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REVOGAB
(Pregabalin)

ریووگیب
(پریگیبلین)

Oral Solution 20 mg/ml

اورل سلوشن ۲۰ ملی گرام/ملی لیٹر

COMPOSITION
Revogab Oral solution 20 mg/mL.

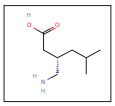
Qualitative and Quantitative Composition
Each ml contains:
Pregabalin.....20mg

Product Description
Physical Properties

Chemical Name:
(S)-3-(aminomethyl)-5-methylhexanoic acid

Molecular Weight
159.23

Structural Formula



Pharmacodynamics and Pharmacokinetics
Pharmacotherapeutic group: Antiepileptics, Other antiepileptics, ATC code: N03AX16
Mechanism of action
In vitro studies show that pregabalin binds to an auxiliary subunit (α2-δ protein) of voltage-gated calcium channels in the central nervous system, potently displacing [3H]- gabapentin. Two lines of evidence indicate that binding of pregabalin to the α2-δ site is required for analgesic and anticonvulsant activity in animal models: ① Studies with the inactive R-enantiomer and other structural derivatives of pregabalin and ② Studies of pregabalin in mutant mice with defective drug binding to the α2-δ protein. In addition, pregabalin reduces the release of several neurotransmitters, including glutamate, noradrenaline, and substance P. The significance of these effects for the clinical pharmacology of pregabalin is not known.
Pregabalin does not show affinity for receptor sites or alter responses associated with the action of several common drugs for treating seizures or pain. Pregabalin does not interact with either GABAA or GABAB receptors; it is not converted metabolically into GABA or a GABA agonist; it is not an inhibitor of acute GABA uptake or degradation.
Pregabalin prevents pain-related behaviors in animal models of neuropathic and postsurgical pain, including hyperalgesia and allodynia. Pregabalin also shows efficacy in animal models of seizures, including maximal electroshock tonic extensor seizures in mice or rats, threshold clonic seizures from pentylenetetrazol, behavioral and electrographic seizures in hippocampal kindled rats, and tonic and clonic seizures in DBA/2 audiogenic mice. Pregabalin does not reduce the incidence of spontaneous absence seizures in Genetic Absence Epilepsy in Rats from Strasbourg (GAERS).

Pharmacodynamic effects
Although the structure of pregabalin is similar to gamma-aminobutyric acid (GABA), it does not bind to GABA receptors. Instead, it binds the alpha2-delta subunit of presynaptic voltage-gated calcium channels in the central nervous system. Pregabalin does not modulate dopamine receptors, serotonin receptors, opiate receptors, sodium channels or cyclooxygenase activity.
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

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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 bioavailability.

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. At clinical doses of 150 to 600 mg/day, the average steady-state plasma pregabalin concentrations were approximately 1.5 and 6.0 µg/mL, respectively.

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 Renantiomer.

Excretion

Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. Renal clearance (CLcr) derived from Phase I studies was 73 mL/min. Page 21 of 24 Pregabalin mean elimination half-life is 6.3 hours. Pregabalin plasma clearance and renal clearance are directly proportional to creatinine clearance (see Special Populations, Renal Impairment). Pregabalin clearance is reduced in patients with impaired renal function).

Linearity/ non-linearity

Pregabalin pharmacokinetics are linear over the recommended daily dose range. Intersubject pharmacokinetic variability for pregabalin is low (< 20%). Multiple dose pharmacokinetics are predictable from single-dose data.

Special Patient Populations

Race

Population pharmacokinetic analyses of the Phase 2/3 studies in patients with chronic pain, general anxiety disorder (GAD) or partial seizures showed that the relationship between daily dose and pregabalin exposure is similar among Caucasians, Blacks and Hispanics.

Gender

Population pharmacokinetic analyses of the Phase 2/3 studies in patients with chronic pain, GAD or partial seizures showed that the relationship between daily dose and pregabalin drug exposure is similar between genders when adjusted for gender-related differences in CLcr.

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. Elderly (> 65 years) 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.

Children and Adolescents

No specific pharmacokinetic studies have been undertaken in patients.

Breast-feeding women

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 average daily infant dose of pregabalin from breast milk (assuming mean milk consumption of 150 mL/kg/day) was 0.31 mg/kg/day, which on a mg/kg basis would be approximately 7% of the maternal dose.

Therapeutic Indications

Indicated for the treatment of neuropathic pain in adults.

Indicated as adjunctive therapy in adults with partial seizures with or without secondary Generalization.

Recommended Dose

Posology

The dose range is 150 to 600 mg (7.5 to 30 ml) per day given in two divided doses. Revogab may be

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taken with or without food.

Neuropathic pain

Pregabalin treatment can be started at a dose of 150 mg (7.5 ml) per day given as two divided doses. Based on individual patient response and tolerability, the dose may be increased to 300 mg (15 ml) per day, given as two divided doses, after an interval of 3 to 7 days, and if needed, to a maximum dose of 600 mg (30 ml) per day after an additional 7-day interval. Since diabetes is frequently complicated by renal disease, patients with diabetic neuropathy, in accordance with current clinical practice, should be assessed for renal impairment prior to commencing Pregabalin and dosage adjusted appropriately. The effectiveness of Pregabalin in the treatment of neuropathic pain has not been assessed in controlled clinical trials for treatment periods longer than 12 weeks. The risks and benefits of treatment to an individual patient should be assessed before extending therapy for longer than 12 weeks.

Epilepsy

Pregabalin treatment can be started with a dose of 150 mg (7.5 ml) per day given as two divided doses. Based on individual patient response and tolerability, the dose may be increased to 300 mg (15 ml) per day given as two divided doses after 1 week. The maximum dose of 600 mg (30 ml) per day given as two divided doses may be achieved after an additional week. It is not necessary to monitor plasma pregabalin concentrations to optimize Revogab therapy. Pregabalin does not alter the plasma concentrations of other commonly used anti-convulsant drugs. Similarly, commonly used anti-convulsant drugs do not alter plasma concentrations of pregabalin.

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.

Special populations

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 individualized according to creatinine clearance (CLcr), determined using the following formula: CLcr (ml/min) = [{140 – age (years)} × weight (kg) 72 × serum creatinine (mg/dL)] (× 0.85 for female patients) Pregabalin is removed effectively form 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.

Hepatic Impairment

No dose adjustment is required for patients with hepatic impairment.

Children and Adolescents (< 18 years)

The safety and effectiveness of pregabalin has not been established in patients below the age of 18 years, with either epilepsy or neuropathic pain.

Elderly (> 65 years)

No dosage adjustment is necessary for elderly patients unless their renal function is compromised.

Method of administration

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

Contraindications

Hypersensitivity to the active substance or to any of the excipients used in the formulation of Revogab oral solution.

Warnings and Precautions

Hereditary Problems of Galactose Metabolism

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Weight Gain

In the controlled studies, weight gain occurred more frequently in patients treated with pregabalin than in patients treated with placebo. Pregabalin associated weight gain was related to dose and length of exposure, but did not appear to be associated with baseline BMI, gender or age. Page 4 of 24 In accordance with current clinical practice, some diabetic patients who gain weight on pregabalin treatment may need to adjust hypoglycemic medications.

Hypersensitivity Reactions

There have been reports in the post-marketing 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 and Somnolence

Pregabalin causes dizziness and somnolence. In the controlled studies, dizziness and somnolence generally began shortly after initiation of pregabalin and occurred more frequently at higher doses. Dizziness and somnolence were the adverse events most frequently leading to withdrawal (4% each) from controlled studies. In pregabalin-treated patients reporting these adverse events in short-term controlled studies, dizziness persisted until the last dose in 31% and somnolence persisted until the

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last dose in 46%. There have also been reports of loss of consciousness, confusion, and mental impairment.

Suicidal Behaviour and Ideation

Antiepileptic drugs (AED), including pregabalin, increase the risk of suicidal thoughts or behaviour in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behaviour, and/or any unusual changes in mood or behaviour.

Substance Misuse, Abuse and Dependence

There have been post-marketing reports of substance misuse and abuse with pregabalin. As with any CNS drug, patients should be carefully evaluated for a history of substance abuse and observed for signs of pregabalin misuse or abuse (e.g., development of tolerance, increase in dose, drug-seeking behaviour).

Renal Failure

Renal failure is a rare adverse reaction to pregabalin. Although the effects of discontinuation on the reversibility of renal failure have not been systematically studied, cases of renal failure have been reported and in some cases discontinuation of pregabalin did show reversibility of this adverse reaction.

Discontinuation

After discontinuation of short-term and long-term treatment with pregabalin withdrawal symptoms have been observed in some patients. The following events have been mentioned: insomnia, headache, nausea, anxiety, hyperhidrosis and diarrhoea.

Congestive Heart Failure

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

Blurred Vision

In controlled studies, a higher proportion of patients treated with pregabalin reported blurred vision than did patients treated with placebo. In the majority of cases, blurred vision resolved with continued dosing. If blurred vision persists, further assessment should be considered.

Post-marketing experience with pregabalin has reported transient visual blurring and other changes in visual acuity. Discontinuation of pregabalin may result in resolution or improvement of these visual symptoms.

Peripheral Oedema

In controlled studies, peripheral oedema occurred more frequently in patients treated with pregabalin than in patients treated with placebo. Peripheral oedema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function. There are limited data on the use of pregabalin in patients with congestive heart failure, and Revogab should be used with caution in these patients.

Creatine Kinase Elevations

Treatment with pregabalin was associated with creatine kinase elevations. Mean changes in creatine kinase from baseline to the maximum value were 60 U/L for pregabalin treated patients and 28 U/L for the placebo patients. In all controlled trials across multiple patient populations, 2% of patients on pregabalin and 1% of placebo patients had a value of creatine kinase at least three times the upper limit of normal. Three pregabalin treated subjects had events reported as rhabdomyolysis in premarketing clinical trials. The relationship between these myopathy events and pregabalin is not completely understood because the cases had documented factors that may have caused or contributed to these events. Pregabalin-AFT should be discontinued if myopathy is diagnosed or suspected or if markedly elevated creatine kinase levels occur.

Opioids

Caution is advised when prescribing pregabalin concomitantly with opioids due to risk of CNS depression. In an observational 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.

Use in the Elderly (>65 years)

Pregabalin treatment has been associated with dizziness and somnolence, which may increase the occurrence of accidental injury (falls) in the elderly population.

Women of childbearing potential/Contraception

Pregabalin use in the first trimester of pregnancy may cause major birth defects in the unborn child. Pregabalin should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the fetus. Women of childbearing potential must use effective contraception during treatment.

Paediatric Use

The safety and effectiveness of pregabalin has not been established in patients below the age of 18 years, with either epilepsy or neuropathic pain.

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Effects on Laboratory Tests

Pregabalin is not known to interfere with any laboratory tests. Some changes in clinical laboratory tests have been noted in patients taking pregabalin.

Interactions with other medicaments

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, pregabalin 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, gabapentin, lorazepam, oxycodone or ethanol. In addition, population pharmacokinetic analysis indicated that the three commonly used drug classes, oral antidiabetics, diuretics and insulin, and the commonly used antiepileptic drugs phenytoin, carbamazepine, valproic acid, lamotrigine, phenobarbital, tiagabine and topiramate, had no clinically significant effect on pregabalin clearance. Similarly, these analyses indicated that pregabalin had no clinically significant effect on the clearance of phenytoin, carbamazepine, valproic acid, lamotrigine, topiramate and phenobarbital.

Co-administration of pregabalin with the oral contraceptives norethisterone and/or ethinylestradiol does not influence the steady-state pharmacokinetics of either agent.

Pregabalin may potentiate the effects of ethanol and lorazepam. In controlled clinical trials, multiple oral doses of pregabalin co-administered with oxycodone, lorazepam, or ethanol did not result in clinically important effects on respiration. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone.

In post-marketing experience, there are reports of respiratory failure, coma and deaths in patients taking pregabalin and other CNS depressant medications, including in patients who are substance abusers. 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.

No specific pharmacodynamic interaction studies were conducted in elderly volunteers.

Pregnancy and lactation

Pregnancy

Australian Category D

Limited clinical data on the use of pregabalin in pregnant women is available and Pregabalin-AFT should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the fetus. Pregabalin use in the first trimester of pregnancy may cause major birth defects in the unborn child. Women of childbearing potential must use effective contraception during treatment.

In a pre- and post-natal study in rats, pregabalin treatment resulted in offspring developmental toxicity at exposures (plasma AUC) ≥ 5 times the expected human exposure at the maximum recommended clinical dose of 600 mg/day. Offspring development was unaffected at 2 times the expected maximum human exposure.

Labour and Delivery

The effects of pregabalin on labour and delivery in pregnant women are unknown. In a pre- and post-natal development study in rats, pregabalin prolonged gestation and induced dystocia at exposures (plasma AUC) approximately 50 times the expected human exposure at the maximum recommended clinical dose of 600 mg/day. These effects were not observed at an exposure that was approximately 12 times the expected human exposure.

Breastfeeding

Pregabalin is excreted in the milk of lactating women. As the safety of pregabalin in infants is not known, breastfeeding is not recommended in women taking Pregabalin-AFT. A decision must be made whether to discontinue breastfeeding or to discontinue Pregabalin-AFT therapy, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility

Preclinical data

In male rats, oral administration of high doses of pregabalin resulted in reversible decreased sperm motility and fertility. These were not observed at exposures (plasma AUC) up to 11 times the expected human exposure at the maximum recommended clinical dose of 600 mg/day. There were also no drug-related effects on sperm parameters in a long-term monkey study with exposures up to 8 times the expected maximum human exposure. In female rats, oestrus cycles were prolonged by high oral doses of pregabalin, but fertility was unaffected, and an increase in post-implantation loss also occurred. No adverse effects were seen at an exposure approximately 50 times the expected maximum human exposure.

Human data

In a double-blind, placebo-controlled clinical trial to assess the effect of pregabalin on sperm motility, 30 of 46 healthy male subjects were exposed to pregabalin at 600 mg/day for 3 months. Pregabalin did not exhibit detrimental effects on the reproductive function of healthy male subjects, as