



Pregabalin & Mecobalamin Capsules

Composition

Each hard gelatin capsule contains:

Pregabalin 75 mg

Mecobalamin 750 mcg

Approved colours used in capsule shell.

Pharmacological properties

Pharmacodynamic properties

Pregabalin

Mechanism of Action:

Pregabalin binds with high affinity to the α_1 -delta site (an auxiliary subunit of voltage-gated calcium channels) in central nervous system tissues. Although the mechanism of action of pregabalin is unknown, results with genetically modified mice and with compounds structurally related to pregabalin (such as gabapentin) suggest that binding to the α_1 -delta subunit may be involved in pregabalin's antinociceptive and antiseizure effects in animal models. In vitro, pregabalin reduces the calcium dependent release of several neurotransmitters, possibly by modulation of calcium channel function. While pregabalin is a structural derivative of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), it does not bind directly to GABA (A) & GABA (B), or benzodiazepine receptors, does not augment GABA(A) responses in cultured neurons, does not alter rat brain GABA concentration or have acute effects on GABA uptake or degradation. However, in cultured neurons prolonged application of pregabalin increases the density of GABA transporter protein and increases the rate of functional GABA transport. Pregabalin does not block sodium channels, is not active at opiate receptors, and does not alter cyclo-oxygenase enzyme activity. It is inactive at serotonin and dopamine receptors and does not inhibit dopamine, serotonin, or noradrenaline reuptake.

Mecobalamin

Mecobalamin is the neurologically active form of vitamin B₁₂, which increases myelin sheath formation and regenerates neurons. Mecobalamin (Methyl-B₁₂) is one of the two forms of biologically active vitamin B₁₂. Methyl-B₁₂ is the principal form of circulating vitamin B₁₂, hence the form which is transported into peripheral tissue. Methyl-B₁₂ is absorbed by the intestine by a specific mechanism which uses the intrinsic factor and by a diffusion process in which approximately 1% of the ingested dose is absorbed. Cyanocobalamin and hydroxycobalamin are forms of the vitamin that require conversion to mecobalamin.

Pharmacokinetic properties

Pregabalin is well absorbed after oral administration.

It is eliminated largely by renal excretion.

It has elimination half-life of about 6 hours.

Absorption and Distribution:

Following oral administration of Pregabalin capsules under fasting conditions, peak plasma concentrations occurs within 1.5 hours. Pregabalin oral bioavailability is $\approx 90\%$ and is independent of dose. Following single (25 to 300 mg) and multiple dose (75 to 900 mg/day) administration, maximum plasma concentration (C_{max}) and area under plasma concentration time curve (AUC) values increase linearly. Following repeated administration, steady state is achieved within 24 to 48 hours. Multiple doses pharmacokinetic can be predicted from single dose data.

The rate of pregabalin absorption is decreased when given with food, resulting in decrease in C_{max} of approximately 25% to 30% and increase in T_{max} to approximately 3 hours. However administration of pregabalin with food has no clinically relevant effect on total absorption of Pregabalin. Therefore, pregabalin can be taken with or without food.

Pregabalin does not bind to plasma proteins. The apparent volume of distribution of pregabalin following oral administration is approximately 0.5 L/kg. Pregabalin is a substrate for system L transporter which is responsible for the transport of large amino acid across the brain barrier. Although there are no data in humans, pregabalin has been shown to cross the placenta in rats and is present in milk of lactating rats.

Metabolism and Elimination:

Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabeled pregabalin, approximately 90% of the administered dose was recovered in urine as unchanged pregabalin. The N-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0.9% of dose. In preclinical studies, pregabalin (S-enantiomer) did not undergo racemization to the R-enantiomer in mice, rats, rabbits or monkey.

Pregabalin is eliminated from systemic circulation primarily by renal excretion as unchanged drug with a mean elimination half life of 6.3 hours in subject with normal renal function. Mean renal clearance was estimated to be 67.0 to 80.9 mL/min in young healthy subjects. Because pregabalin is not bound to plasma proteins this clearance rate indicates that renal tubular reabsorption is involved. Pregabalin elimination is nearly proportional to creatinine clearance.

Indications

Management of neuropathic pain associated with diabetic peripheral neuropathy.

Management of post herpetic Neuralgia.

Adjunct therapy for adult patient with partial onset of seizures.

Management of Fibromyalgia.

Posology and method of administration

Route of administration: Oral use

Pregabalin and Mecobalamin capsules can be taken with or without food. Dose may be increased up to 300 mg pregabalin/day within one week based on efficacy and tolerability. Dose need not to be adjusted in case of renal dysfunction.

Contraindications

Pregabalin and Mecobalamin capsules are contra-indicated in patients with known hypersensitivity to pregabalin or mecobalamin or any of its components. Angioedema and hypersensitivity reactions have occurred in patients receiving pregabalin therapy.

Warnings and precautions for use

Pregabalin

Angioedema and hypersensitivity may occur. Withdraw pregabalin gradually to minimize the potential of increased seizure frequency in

patients with seizure disorders. Increases the risk of suicidal thoughts or behavior. May cause peripheral edema, dizziness, somnolence and weight gain. Following abrupt or rapid discontinuation, patients have reported symptoms including insomnia, nausea, headache, and diarrhea. Taper gradually over a minimum of 1 week. High incidence of hemangiosarcoma was identified in two different strains of mice when administered pregabalin. Clinical significance of this finding is unknown. Inform patients to notify their physician if changes in vision occur. Discontinue treatment with pregabalin if myopathy is diagnosed or suspected or if markedly elevated creatine kinase levels occur. May cause decrease in platelet count and PR interval prolongation.

Mecobalamin

Should not be used for > 1 month in patients if no clinically therapeutic outcome is observed. Susceptible to photolysis, hence caution should be taken so as not to expose the capsules to direct light.

Drug interactions

Pregabalin

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

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

Mecobalamin

These may cause side effects, but many people have no, or minor, side effects. Check with your doctor if any of these most COMMON side effects persist or become bothersome:

Bloated feeling; headache; itching; mild diarrhea; mild fever; nausea; vomiting.

Seek medical attention right away if any of these SEVERE side effects occur:

Severe allergic reactions (rash; hives; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue); lower back or side pain.

Pregnancy and lactation

Pregnancy

Anti-epileptic drugs (AEDs) have the potential to affect fetal development throughout pregnancy. Considering the broad therapeutic indications of pregabalin (PGB) and its potential teratogenic effects, it's advisable to avoid this drug during pregnancy.

Lactation

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.

Side effects

Pregabalin

The common adverse effects of pregabalin are dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, and "thinking abnormal" (primarily difficulty with concentration/attention).

Mecobalamin

Mecobalamin is relatively safe and devoid of side effects. Could infrequently cause pulmonary oedema, CHF, peripheral vascular thrombosis, polycythemia vera, mild transient diarrhea, itching, transitory exanthema, feeling of swelling of entire body.

Overdosage and its Treatment

Pregabalin seems to be relatively benign in overdose. There is a report of an overdose where 8 grams of Pregabalin were taken with no clinically unexpected effects arising, and a report of an 11.5 gram overdose with more serious consequences. General supportive care of the patient is indicated, and in overdose side effects such as agitation, coma, seizures, haemopoietic suppression, sinus tachycardia, and urinary retention are possible.

Treatment or Management of Overdose

There is no specific antidote for overdose with pregabalin. If indicated, elimination of unabsorbed drug may be attempted by emesis or gastric lavage; usual precautions should be observed to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient.

Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment. Standard hemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours).

Storage condition

Store below 30°C. Protect from light and moisture. Keep the medicine out of reach of children.

SHELF LIFE: 24 months

PRESENTATION: 1 Blister of 10 Capsules and 3 Blisters of 10 Capsules in a printed carton with a package insert.

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