NEUROGLIN

Each capsule contains

Pregabalin ……..…75 mg

Methylcobalamin …….….1500 mcg

Dosage Form

Capsules

Pharmacology

Pharmacodynamics

Pregabalin

Pregabalin is a structural derivative of the inhibitory neurotransmitter, gamma-aminobutyric acid (GABA). Pregabalin 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 binds with high affinity to the $alpha_2$-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 $alpha_2$-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.

Pregabalin does not block sodium channels, is not active at opiate receptors, and does not alter cyclooxygenase enzyme activity. It is inactive at serotonin and dopamine receptors and does not inhibit dopamine, serotonin, or noradrenaline reuptake.

Methylcobalamin

Methylcobalamin (Mecobalamin, MeCbl), is one of the two biologically active vitamin B12. Mecobalamin acts as an important cofactor in the reaction of one class of the B12 enzymes, the methyltransferases. The B12-dependent methyltransferases play an important role in amino acid metabolism in many organisms as well as in one-carbon metabolism and CO_2 fixation in anaerobic microbes. Among them, methionine synthase is the most extensively studied B12-dependent methyltransferase in humans. As the cofactor of the enzyme methionine synthase, mecobalamin functions to catalyse the transfer of the methyl group from methylene tetrahydrofolate to homocysteine (Hcy) to form methionine and tetrahydrofolate.

Because mecobalamin acts as an important cofactor of methionine synthesis, supplements of mecobalamin enhance the efficiency of the remethylation pathway, consequently accelerating Hcy consumption and reducing its concentration. Thus, lowering homocysteine concentrations to the

normal range (4 – 15 μmol/l) seems to be an effective therapeutic method in decreasing the risks of the diseases mentioned above.

In an animal study, intragastric administration of mecobalamin was also found to improve the arterial baroreflex function, which is a new target for the prevention of stroke in stoke-prone, spontaneously hypertensive rats. It was also postulated that the reduction of homocysteine concentration might contribute to the baroreflex sensitivity, thus improving the effect of mecobalamin.

Deficiency of vitamin B 12 results in the lack of mecobalamin and has been associated with significant neurological pathology, especially peripheral neuropathy. In an *in vitro* study, chronic administration of mecobalamin protected cultured retinal neurons against NMDA-receptor-mediated glutamate neurotoxicity, probably by altering the membrane properties through SAM-mediated methylation. It was also suggested that altered membrane properties induced by SAM-mediated methylation is the major route of the neuroprotective effect of mecobalamin in several types of CNS insults.

Pharmacokinetics

Pregabalin

Pregabalin is well absorbed after oral administration, is eliminated largely by renal excretion and has an elimination half-life of about 6 hours.

Absorption

Following oral administration of pregabalin capsules under fasting conditions, peak plasma concentrations occur within 1.5 hours. Pregabalin oral bioavailability is ≥ 90% and is independent of dose. Following single - (25 to 300 mg) and multiple- dose (75 to 900 mg/day) administration, maximum plasma concentrations (C_{max}) and area under the plasma concentration-time curve (AUC) values increase linearly. 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} of approximately 25% to 30% and an increase in T_{max} to approximately 3 hours. However, administration of pregabalin with food has no clinically relevant effect on the total absorption of pregabalin. Therefore, pregabalin can be taken with or without food.

Distribution

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 acids across the blood brain barrier. Although there are no data in humans, pregabalin has been shown to cross the blood brain barrier in mice, rats, and monkeys.

Metabolism

Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabeled pregabalin, approximately 90% of the administered dose was recovered in the urine as 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, pregabalin (S-enantiomer) did not undergo racemization to the R-enantiomer in mice, rats, rabbits, or monkeys.

Excretion

Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug with a mean elimination half-life of 6.3 hours in subjects 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 (CLcr).

Special populations

Geriatrics

Pregabalin oral clearance tended to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with age-related decreases in CLcr. Reduction of pregabalin dose may be required in patients who have age-related compromised renal function

Gender

Population pharmacokinetic analyses of the clinical studies showed that the relationship between daily dose and pregabalin drug exposure is similar between genders.

Renal impairment and haemodialysis

Pregabalin clearance is nearly proportional to creatinine clearance (CLcr). Dosage reduction in patients with renal dysfunction is necessary. Pregabalin is effectively removed from plasma by haemodialysis. Following a 4-hour haemodialysis treatment, plasma pregabalin concentrations are reduced by approximately 50%. For patients on haemodialysis, dosing must be modified.

Paediatric Pharmacokinetics

Pharmacokinetics of pregabalin has not been adequately studied in paediatric patients.

Methylcobalamin
Absorption

Evidence indicates methylcobalamin is utilized more efficiently than cyanocobalamin to increase levels of one of the coenzyme forms of vitamin B12. Experiments have demonstrated similar absorption of methylcoblamin following oral administration. The quantity of cobalamin detected following a small oral dose of mecobalamin is similar to the amount detected following the administration of cyanocobalamin, but significantly more cobalamin accumulates in liver tissue, which is associated with mecobalamin intake.

Distribution and Metabolism

Cobalamin circulates in plasma bound to two carrier proteins: transcobalamin (TC) and haptocorrin. TC is a 43-kDa non-glycoprotein that transfers cobalamin from the intestine into the blood stream

and then into all the cells of the body. Cobalamin-saturated transcobalamin (holoTC) constitutes 6 – 20% of total plasma cobalamin. The unsaturated TC is called apotranscobalamin, which constitutes the major part of TC. Additionally, total homocysteine (tHcy) and methylmalonic acid are considered to be two functional markers of vitamin B 12 status in adults.

Excretion
Human urinary excretion of methylcobalamin is about one third that of a similar dose of cyanocobalamin, indicating substantially greater tissue retention.

Indications

NEUROGLIN is indicated for the treatment of peripheral neuropathic pain in adults.

Dosage and Administration

NEUROGLIN is given orally with or without food.
The dose range for pregabalin is 150 to 300 mg per day given in two or three divided doses. The dosage range for methylcobalamin for clinical effectiveness is 0.5-6 mg/day, and no significant therapeutic advantage is observed beyond this range. However, the most commonly used dose was 0.5 – 1.5 mg/day administered orally.

NEUROGLIN treatment can be started at a dose of two capsules b.i.d. Based on individual patient response and tolerability, the dosage may be increased to 4 capsules in two divided doses after an interval of 3 to 7 days.

Discontinuation of pregabalin

If NEUROGLIN has to be discontinued, it is recommended this should be done gradually over a minimum of 1 week.

Patients with renal impairment

In view of dose-dependent adverse events and since pregabalin is eliminated primarily by renal excretion, the dose should be adjusted in patients with reduced renal function. Dosage adjustment in patients with renal impairment should be based on creatinine clearance (CLcr), as indicated in Table 1, determined by the following formula:

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