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Gabapentin and Methylcobalamin Tablets

GABIL™

Composition:
Each film-coated tablet contains
Gabapentin USP 300 mg
Methylcobalamin 500 mcg
Excipients qs

Description :
Neuropathic pain of varied etiology is caused by a primary lesion or dysfunction in the nervous system, where pain is a primary manifestation. Stuides have revealed that disorders of the myelin in both the CNS and the PNS is a feature in majority of the neuropathies. There is demyelination of the spinal cord, brain, optic and peripheral nerves leading to cell degeneration, loss of nerve function and finally damaged nerve fibers. Gabapentin prevents pain-related responses in neuropathic pain.

Methylcobalamin improves nerve function by contributing to nervemyelination, stimulate protein synthesis for neural regeneration and repair In peripheral neuropathies, regenerate neurons and myelin sheath that protect nerve axons and peripheral nerve thereby facilitating normal cell growth.

Gabapentin : Gabapentin is described as 1 (aminomethy lcyclohexaneaceticacid) with a molecular formula of C2H2NO2 and a molecular weight of 171.24.
Methylcobalamin : Methylcobalamin is one of the two coenzyme forms of vitamin B12 (the other being adenosylcobalamin). It is a cofactor in the enzyme methionine synthase which functions to transfer methyl groups of the regeneration of methionine from homocysteine. Indication : For the treatment of neuropathic pain in adults.

Clinical Pharmacology:
Gabapentin: Gabapentin is structurally related to the neurotransmitter GABA (Gamma Amino Butyric Acid) but doses not interact with GABA receptors, it is not metabolized to GABA or to GABA agonists, and is not an inhibitor of GABA uptake or degradation. The mechanism by which Gabapentin exerts its analgesic action is unknown, but in animal models of analgesia, Gabapentin prevents allodynia (Pain related behaviour in response to a normally innocuous stimulus) and hyperalgesia (exaggerated response to painful stimuli). iIn particular, Gabapentin prevents pain related responses in several animal models of neuropathic pain (eg :spinal nerve ligation models, streptozocin-induced diabetes models, spinal cord injury model, acute Herpes Zoster infection model). Gabapentin also decreases pain related responses after peripheral inflammation. Gabapentin bioavailability is not dose proportional, i.e. as dose is increased, bioavailability decreases. Food has only a slight effect on the rate and extent of of absorption of Gabapentin. Less than 3% of Gabapantin circulates bound to plasma protein. Gabapentin is eliminated from the systemic circulation by renal excretion as unchanged drug. Half life is 5 to 7 hrs and is unaltered by dose or following multiple dosing. Gabapentin is not appreciably metabolized in humans nor does it interferes with the metabolism of commonly co administered antiepileptic drugs.

Gabapentin pharmacokinetics is not affected by repeated administration.
Elderly patients and patients with impaired renal function : Gabapentin plasma clearance is reduced. Dose adjustment is patients with compromised renal function or undergoing heamodialysis is recommended.
Heamodialysis : Heamodialysis has a significant effect on Gabapentin elimination in anuric subjects. Dose adjustment is patients undergoing heamodialysis is necessary.
Hepatic disease : Since Gabapentin is not metabolized, no study is available on hepatic impairment.
Peadiatric patients : The pharmacokinetic data reveals that the effective daily dose in peadiatric patients with epilepsy aged 3 to 4 years should be 40mg/kg/ day to achieve average plasma concentrations similar to those achieved in patients 5 years of age and older receiving Gabapentin at 30mg kg/day.

Methylcobalamin :
Vitamin B12 is necessary for the formation of blood corpuscles, nerve sheaths and various proteins. It is also involved in fat and carbohydrate metabolism and is essential for growth.

Adenosylcobalamin is the co enzyme for isomerization of 1-Methylmalonyl Co enzyme A to Succinyl Coenzyme A (an important reaction in lipid and carbohydrate metabolism) and in Ribonucleotide reduction (which provides building blocks for DNA synthesis). Reactions involving methylcobalamin include biosynthesis of methionine, methane and acetate. There is evidence that Vitamin B12 is required the synthesis of folate polyglutamase (active coenzyme required in the formation of nerve tissue) and in the regeneration of folate during red blood cell formation.

Methylcobalamin is an endogenous Coenzyme B12 Methylcobalamin plays as important role in transmethylation as a coenzyme of methionine synthetase in the synthesis of methionine from homocystnine.

Methylcobalamin is well transporter to nerve cells organelles, and promotes nucleic acid and protein synthesis in animal studies : Methylcobalamin was shown to be better transporter to nerve cell organelles than cyanocobalamin.
It has also been shown in experiments with cells from the brain origin and spinal nerve calls to be involved in the synthesis of thymidine from deoxyuridine, promotion of deposited folate utilization and metabolism of nucleic acid. Also, methylcobalamin plays role in nucleic acid and protein synthesis more than adenosylcobalamin does.
Methylcobalamin promotes axonal transport and axonal regeneration : Methylcobalamin normalizes axonal skeletal protein transport in sciatic nerve cells from rat models with streptozotocin-induced diabetes mellitus. It exhibits neuropathologically and electrophysiologically inhibitory effects on nerve degeneration in neuropathies induced by drugs, such as adriamycin, acrylamide, and vincristine, models of axonal degeneration in mice and neuropathies in rats with spontaneous diabetes mellitus. Methylcobalamin promotes myelination (phospholipids synthesis) : Methylcobalamin promotes the synthesis of lecithin, the main constituent of medullary sheath lipids, and increases myelination of neurons in tissue culture more than adenosylcobalsmin does.
Methylcobalamin resotes delayed synaptic transmission and diminished neurotransmitters to normal in animal studies : methylcobalamin restores end-plate potential induction early by addition, methylcobalamin normalizes diminished brain tissue levels of acetyl choline in rats fed a choline dificient diet.

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 methylcobalamin following oral administration. The quantity of cobalamin detected following a small oral dose of methylcobalamin is similar to the amount following administration of cyanocobalamin; but significantly more cobalamin accumulates in liver tissue following administration of methylcobalamin. Human urinary excretion of methylcobalamin is about one third that of a similar dose of cyanocobalamin, indicating substantially greater tissue retention.

Contraindication :
Hypersensitivity to cobalamin products or cobalt or Gabapentin or any component of the preparation.
Tobacco amblyopia. Should not be used to treat megaloblastic anaemia of pregnancy. Should not be administered before perncious anaemia or folate deficiency has been ruled out.

Precautions and Warnings :
Keep out of reach of children.

Gabapentin :
Gabapentin may cause dizziness, somnolence and other symptoms and signs of CNS depression. Accordingly, patients who are on the drug should be advised neither to drive a car nor to operate other complex machinery until they have gained sufficient experience on the drug to gauge the effects of the drug on their mental and/or motor performance adversely.

Patients who require concomitant treatment with morphine may experience increases in Gabapentin concentrations. Patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of Gabapentin or morphine should be reduced appropriately.

Drug withdrawal :
Antiepileptic drugs should not be abruptly discontinued because of the possibility of increasing seizure frequency in patients with epilepsy.

Tumorigenic Potential :
Clinical experience during Gabapentin's premarketing development provides no direct means to assess its potential for inducing tumors in humans. It is reported that in clinical studies in adjunctive therapy in epilepsy comprising 2085 patients-years of exposure in patients> 12 years of age, new tumors were reported in 10 patients (2breast, 3 brain, 2 lungs, 1 adrenal, 1 non-Hodgkin's lymphoma, 1 endometrial carcinoma in situ), and preexisting tumors worsened in 11 patients (9 brain, 1 breast, 1 prostate) during or upto 2 years following discountinuation of Gabapentin.

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Without knowledge of the background incidence and recurrence in a similar population not treated with Gabapentin, it is impossible to know whether the incidence seen in this cohort is or is not affected by treatment.Carcinogenesis, mutagenesis, impairment of fertility : The carcinogenic risk of Gabapentin in humans is unclear, Gabapentin was not found to have mutagenic or genotoxic potential and it also had no adverso effect on fertility or reproduction in animal studies. Pregnancy : This drug should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in nursing mothers :
Gabapentin should be used in women who are nursing only if the benefits clearly outweight the risks.

Pediatric use :
Safety and effectiveness of Gabapentin in the management of postherpetic neuralgia have not been established.
Methylcobalamin : The prolonged use of larger doses of methylcobalamin is not recommended for patients whose occupation requires the handling of mercury or mercury compounds..
Use cautiously in patients with hypertension, cardiovascular and lung diseases..Cardiac arrhythmias secondary to hypokalaemia during initial therapy have been reported. Vitamin B12 should be given prophylactically only when there is a reasonable indication. .Administration of methycobalamin doses greater than 10mcg daily, may produce a hematological response in patients with folate deficiency. It is important to monitor methylcobalamin concentrations in plasma and to obtain peripheral blood counts at intervals of 3 to 6 months to confirm that adequacy of therapy. Since refractoriness to therapy can develop at any time, evaluation must continue throughout the patient's life. Serum concentrations may be decreased by concurrent administration of oral contraceptives. Blood concentrations of methylcobalamin may be reduced if large doses of folate are taken continuously.

Drug Interactions :
Gabapentin : Gabapentin is not appreciably metabolized nor does in interfere with the metabolism of commonly co administered antiepileptic drugs.

Hydrocodone : Co administration of Gabapentin decreases hydro codone Cmax and AUC values in a dose-dependent manner relative to the administration of hydrocodone alone; hydrocodone increases Gabapentin AUC values by 14%.
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Morphine : Patients who require concomitant treatment with morphine may experience increases in Gabapentin concentrations. Patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of Gabapentin or morphine should be reduced appropriately..

Cimetidine :
Cimetidine appeared to alter the renal excretion of both Gabapentin and creatinine, an endogenous marker of renal function. The effect of Gabapentin on cimetidine was not evaluated..
Oral contraceptive : The Cmax of northindrone was reported to be 13% higher whenit was co administered with Gabapentin this interaction is not expected to be of clinical importance.
Antacid :
It is recommended that Gabapentin be taken atleast two hours following administration of an antacid.

Effect of probenecid : Probenecid is a blocker of renal tubular secretion, Gabapentin pharmacokinetic parameters without and with probenecid were comparable. This indicates that Gabapentin doses not undergo renal tubular secretion by the pathway that is blocked by probenecid.

Methylcobalamin :
Tetracycline : Vitamin B12 should not be taken at the same time as the antibiotic Tetracycline because it Interferes with the absorption and effectiveness of this medication. Vitamin B12 either alone or in combinatin with other B vitamins should be taken at different times of the day from tetracycline.

Chemotherapy Medications :
Blood levels of Vitamin B12 may be reduced when taking chemotherapy medications (particularly methotrexate) for cancer.
Absorption of cobalamin is impaired by alcohol, vitamin B6 (pyridoxine) deficiency, cholestyramine, para-aminosalicylic acid colchicines, neomycin, the oral bigunades, metformin, histamine H2 receptor antagonists (clmetidine, ranitidine, etc.) phenformin and possibly potassium chloride. A number of anticonvulsants-phenobarbitone, primidone, phenytoin, and ethylphenacemidecan alter the metabolism of cobalamin in the cerebrospinal fluid and lead to neuropsychotic disturbances. Several substituted amide, lactone and lactum analogues of cyanocobalamin compete with binding sites on intrinsic factor and lead to depressed absorption of the vitamins. Nitrous oxide also interferes with cobalamin metabolism.

Adverse effects :
Gabapentin : The infrequently reported adverse events include confusion, depression, chest pain, cellulites, malaise, face edema, allergic reaction, abscess, chills and fever, hypertension, syncope, palpitaion, migraine, phypotension, peripheral vascular disorder, abnormal stools, anorexia, diabetes mellitus, asthenia, infection, headache, abdominal pain, diarrhea, dry mouth, constipation, nausea, vomiting, flatulence, peripheral adema, weight gain, hyperglycemia, dizziness, somnolence, ataxia, abnormal thinking, abnormal gait, incoordination, amnesia, hypoesthesia, pharyngitis rash, amblyopia, conjunctivitis, diplopia, otitis media, ecchymose aneamia, hypoglycemia, weight loss, arthralgia, myalgia, leg cramps, vertigo, nervousness, neuropathy, anxiety, rhinitis, pneumonia, pruritus, skin ulcer, dry skin, Herpes zoster, fungal dermatilis, urticaria, abnormal vision, taste perversion, deafness, urinary tract infection, dysuria, impotence, polyuria etc.

Methylcobalamin :
Generally well tolerated.

Overdose Management :
Gabapentin : Acute oral overdoses of Gabapentin upto 43 gms have been reported. In these cases double vision, slurred speech, drownsiness, lethargy, and diarrhea were observed. All patients recovered with supportive care, Gabapentin can be removed by haemodialysis.

Methycobalamin :
No such case have been described in the literature and it is unlikely that any harm would result.

Dosage and Administration :
The drug should be given as directed by the physician. The general recommended therapy is to start as one tablet, single dose, on Day 1. Two tablets (Divided b.i.d) on Day 2. and three tablets (dlvided t.i.d) on Day 3. The dose may then be uptitrated up to 2 tablets, 3 times a day. The average effective dose of methylcobalamin has been found to be 1500 mcg/day which is achieved by giving atleast 3 tablets a day.

How supplied :
Strip of 10 tablets

Storage :
Store in a cool, dry place. Protect from light.

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