SCOTT-EDIL
Enhancing Life

SCOTT-EDIL PHARMACIA LTD.

56, E.P.I.P Phase –I, Jharmajri, Baddi, Distt. Solan-173205 (HP) , India

Summary of Product Characteristics (SPC)

1. Name of the medicinal product

AKOBAL-G® (Gabapentin & Methylcobalamin Tablets)

1.1 *International Non-Proprietary Name (INN)*

Gabapentin & Methylcobalamin Tablets

1.2 *Strength*

300 mg/500 mcg

1.3 *Pharmaceutical form*

Oral Solid Dosage Form

2. Qualitative and quantitative composition

Each film coated tablet contains:
Gabapentin USP 300 mg
Methylcobalamin USP 500 mcg
Excipients q.s.
Colour: Ponceau 4R

3. Pharmaceutical form

Film Coated Tablets

Visual Description: Dark Pink coloured, elongated, biconvex, film coated tablet, having a mid break line on one side and plain on other side.

4. Clinical particulars

4.1 Therapeutic indications

Akobal-G® is efficaciously indicated in the following conditions:

- Diabetic Neuropathic pain;
- Trigeminal Neuralgia;
- Alcohol induced Neuropathy Peripheral Neuropathy;
- Peripheral Neuropathy;
- Generalised Anxiety disorders;
- Partial Seizures
- Hyperneurotransmission;
- Dysthesias and Spastic pain;
- Nerve fibers insulation and Regeneration of damaged Neurones.

4.2 Posology and method of administration

Posology

One to three tablets daily up to six weeks or as directed by Registered Physician/Clinical Pharmacist.

AKOBAL-G® is given orally with or without food.

Method of administration

Oral

4.3 Contraindications

Hypersensitivity, Lactation, Pregnancy, Driving, Working with machines and other activities that require alertness.

4.4 Special warnings and precautions for use

WARNINGS
AKOBAL-G® may cause Peripheral Oedema, decreased platelet count and prolonged PR interval.
Keep out of children's reach. Regular vision checks recommended.

PRECAUTIONS
Discontinue therapy if patients develop severe angioedema, Withdrawal of therapy should be gradual over at least seven days.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent administration AKOBAL-G® with Morphine, Oxycodeine Lorazepam and Ethanol may increase the CNS effects.

Antacids: AKOBAL-G® is recommended to be taken at least two hours following administration of an Antacid.

Tetracyclines: Methylcobalamine absorption and tetracycline effectiveness is adversely affected by tetracycline.

4.6 Pregnancy and lactation

Pregnancy

Risk related to epilepsy and antiepileptic medicinal products in general. The risk of birth defects is increased by a factor of 2 – 3 in the offspring of mothers treated with an antiepileptic medicinal product. Most frequently reported are cleft lip, cardiovascular malformations and neural tube

defects. Multiple antiepileptic drug therapy may be associated with a higher risk of congenital malformations than monotherapy, therefore it is important that monotherapy is practised whenever possible. Specialist advice should be given to women who are likely to become pregnant or who are of childbearing potential and the need for antiepileptic treatment should be reviewed when a woman is planning to become pregnant. No sudden discontinuation of antiepileptic therapy should be undertaken as this may lead to breakthrough seizures, which could have serious consequences for both mother and child. Developmental delay in children of mothers with epilepsy has been observed rarely. It is not possible to differentiate if the developmental delay is caused by genetic, social factors, maternal epilepsy or the antiepileptic therapy.

Risk related to gabapentin

There are no adequate data from the use of gabapentin in pregnant women.

Studies in animals have shown reproductive toxicity.The potential risk for humans is unknown. Gabapentin should not be used during pregnancy unless the potential benefit to the mother clearly outweighs the potential risk to the foetus.

No definite conclusion can be made as to whether gabapentin is associated with an increased risk of congenital malformations when taken during pregnancy, because of epilepsy itself and the presence of concomitant antiepileptic medicinal products during each reported pregnancy.

Breastfeeding

Gabapentin is excreted in human milk. Because the effect on the breast-fed infant is unknown, caution should be exercised when gabapentin is administered to a breast-feeding mother. Gabapentin should be used in breast-feeding mothers only if the benefits clearly outweigh the risks.

Fertility

There is no effect on fertility in animal studies.

4.7 Effects on ability to drive and use machines

Gabapentin may have minor or moderate influence on the ability to drive and use machines. Gabapentin acts on the central nervous system and may cause drowsiness, dizziness or other related symptoms. Even, if they were only of mild or moderate degree, these undesirable effects could be potentially dangerous in patients driving or operating machinery. This is especially true at the beginning of the treatment and after increase in dose

4.8 Undesirable effects

The infrequently reported ADRs are: Drowsiness, Dizziness, Visual Disturbance, Ataxia, Tremor, Lethargy, Memory imparment, Euphoria, Weight gain, Constipation, Dry mouth, Peripheral Oedema, Depression, Confussion and agitation.

4.9 Overdose

Gabapentin: Acute oral overdoses of Gabapentin up to 43 gm have been reported. In these cases double vision, slurred speech, drowsiness, lethargy, and diarrhea were observed. All patients recovered with supportive care, Gabapentin can be removed by haemodialysis.

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

5. Pharmacological properties

Pharmacotherapeutic groups: Antiepileptics, Other antiepileptics ATC code: N03AX12

5.1 Pharmacodynamic properties

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 behavior in response to a normally innocuous stimulus) and hyperalgesia (exaggerated response to painful stimuli). in 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.

5.2 Pharmacokinetic Properties

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 Gabapentin 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 or 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 Methylcobal amin 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 deficient 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.

5.3 Preclinical safety data

Carcinogenesis

Gabapentin was given in the diet to mice at 200, 600, and 2000 mg/kg/day and to rats at 250, 1000, and 2000 mg/kg/day for two years. A statistically significant increase in the incidence of pancreatic acinar cell tumours was found only in male rats at the highest dose. Peak plasma drug concentrations in rats at 2000 mg/kg/day are 10 times higher than plasma concentrations in humans given 3600 mg/day. The pancreatic acinar cell tumours in male rats are low-grade malignancies, did not affect survival, did not metastasise or invade surrounding tissue, and were similar to those seen in concurrent controls. The relevance of these pancreatic acinar cell tumours in male rats to carcinogenic risk in humans is unclear.

Mutagenesis Gabapentin demonstrated no genotoxic potential. It was not mutagenic in vitro in standard assays using bacterial or mammalian cells. Gabapentin did not induce structural chromosome aberrations in mammalian cells in vitro or in vivo, and did not induce micronucleus formation in the bone marrow of hamsters.

Impairment of Fertility No adverse effects on fertility or reproduction were observed in rats at doses up to 2000 mg/kg (approximately five times the maximum daily human dose on a mg/m2 of body surface area basis).

Teratogenesis

Gabapentin did not increase the incidence of malformations, compared to controls, in the offspring of mice, rats, or rabbits at doses up to 50, 30 and 25 times respectively, the daily human dose of 3600 mg, (four, five or eight times, respectively, the human daily dose on a mg/m2 basis).

Gabapentin induced delayed ossification in the skull, vertebrae, forelimbs, and hindlimbs in rodents, indicative of fetal growth retardation. These effects occurred when pregnant mice received oral doses of 1000 or 3000 mg/kg/day during organogenesis and in rats given 500, 1000, or 2000 mg/kg prior to

and during mating and throughout gestation. These doses are approximately 1 to 5 times the human dose of 3600 mg on a mg/m2 basis.

6. Pharmaceutical particulars

6.1 List of excipients

Microcrystalline Cellulose PH-102
Povidone K-30
Isopropyl Alcohol
Talc
Sodium Starch Glycolate
Colloidal Silicon Dioxide
Croscarmellose Sodium
Magnesium Stearate
AF Coat Non Aqueous Extra White
Ponceau 4R
Dichloromethane
Isopropyl Alcohol

6.2 Incompatibilities

None Known.

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store in a cool and dry place at a temperature not exceeding 30°C. Protect from light.

6.5 Nature and contents of container

10 x 1 x 10 Tablets Alu-Alu pack

6.6 Special precautions for disposal and other handling

None Known.

7. Manufactured By

Scott-Edil Pharmacia Limited,
56, EPIP, Phase-I, Jharmajri,
Baddi, Distt. Solan- 173205 (H.P)
INDIA

8. Marketed By

Akol Healthcare Ltd.

9. Date of revision of the text

Not applicable

10. DOSIMETRY (IF APPLICABLE)

Not applicable

11. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

Not Applicable