Summary Product Characteristics (SPC)

Product Information for Health Professionals

(Invented) Name of the Medicinal Product

BIOPENTIN (Gabapentin 300 mg & Methylcobalamin 500mcg Tablets)

Strength: Gabapentin 300 mg & Methylcobalamin 500mcg.

Pharmaceutical Form

Tablets [film coated]

Qualitative and Quantitative Composition

Each film coated tablet contains:

Gabapentin USP 300 mg

Methylcobalamin 500mcg

Excipients qs.

Colour: Sunset Yellow & Titanium Dioxide BP

Pharmaceutical Form

Light Orange coloured, circular, biconvex film coated tablets, break line on one side and plain on other side.

Clinical Particulars

Therapeutic Indications

BIOPENTIN Tablets are indicated for the treatment of Diabetic and non-diabetic neuropathic pain and Postherpetic neuralgia.

Posology and Method of Administration

BIOPENTIN is given orally with or without food. If dose is reduced, discontinued or substituted with an alternative medication, this should be done gradually over a minimum of 1 week (a longer period may be needed at the discretion of the prescriber).

The general recommended therapy is to start as one tablet per day on day 1, one tablet each two times a day on day 2, and one tablet each three times a day on day 3. The dose may then be up titrated up to one tablet each three times a day. The average effective dose of methylcobalamin has been found to be 1500mcg/day which is achieved by giving at least 3 tablets per day.

Contraindications

Hypersensitivity to cobalamin products or Gabapentin or any component of the preparation.

Tobacco amblyopia. Should not be administered before pernicious anemia or folate deficiency has been ruled out.

Gabapentin is contraindicated in Breast-feeding, Pregnancy, Carcinogenicity, when driving and with alcohol. For Methylcobalamin there are no independent and relative contraindications

Special Warnings and Precautions for use

Gabapentin should be used with caution in patients with a history of psychotic illness and in renal impairment. The manufacturer recommends dosage reduction in patients with reduced renal function or those undergoing haemodialysis. False positive readings have been reported with some urinary protein tests in patients taking gabapentin. Care is required when withdrawing gabapentin therapy.

Interaction with other Medicinal Products and other forms of interaction

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%.

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 B_{12} should not be taken at the same time as the antibiotic Tetracycline because it interferes with the absorption and effectiveness of this medication. Vitamin B_{12} either alone or in combination 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.

The clinical studies have demonstrated the absence of interaction with the drugs such as: warfarin, tolbutamide, aspirin (acetylsalicylic acid), chlorpromazine, indomethacin.

Pregnancy and Lactation

Pregnancy

Gabapentin has been shown to be fetotoxic in rodents, but this is not necessarily predictive of human toxicity. No studies of its use in human pregnancy exist, and it should be used in this condition only if the benefits outweigh the potential risks. Transfer of gabapentin to breast milk is extensive, but plasma concentrations appear to be low in suckling infants and no adverse effects have been observed in the newborn.

Methylcobalamin Safety in pregnancy has not been established.

Lactation

Transfer of gabapentin to breast milk is extensive, but plasma concentrations appear to be low in suckling infants and no adverse effects have been observed in the newborn.

Methylcobalamin Safety in breast feeding has not been established.

Undesirable effects

Postherpetic Neuralgia

The most commonly observed adverse events associated with the use of Gabapentin in adults, not seen at an equivalent frequency among placebo-treated patients, were dizziness, somnolence, and peripheral edema.

In the 2 controlled studies in postherpetic neuralgia, 16% of the 336 patients who received Gabapentin and 9% of the 227 patients who received placebo discontinued treatment because of an adverse event. The adverse events that most frequently led to withdrawal in Gabapentin-treated patients were dizziness, somnolence, and nausea.

Epilepsy

The most commonly observed adverse events associated with the use of Gabapentin in combination with other antiepileptic drugs in patients > 12 years of age, not seen at an equivalent frequency among placebo-treated patients, were somnolence, dizziness, ataxia, fatigue, and nystgmus. The most commonly observed adverse events reported with the use of Gabapentin in combination with other antiepileptic drugs in pediatric patients 3 to 12 years of age, not seen at an equal frequency among placebo-treated patients, were viral infection, fever, nausea and/or vomiting, somnolence, and hostility.

Approximately 7% of the 2074 patients > 12 years of age and approximately 7% of the 449 pediatric patients 3 to 12 years of age who received Gabapentin in premarketing clinical trials discontinued treatment because of an adverse event. The adverse events most commonly associated with withdrawal in patients > 12 years of age were somnolence (1.2%), ataxia (0.8%), fatigue (0.6%), nausea and/or vomiting (0.6%), and dizziness (0.6%). The adverse

events most commonly associated with withdrawal in pediatric patients were emotional liability (1.6%), hostility (1.3%), and hyperkinesia (1.1%).

No adverse events observed or toxic effects even at high dose for long term with Methylcobalamin.

Overdose

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

Pharmacological Properties

PHARMACODYNAMIC

Pharmacotherapeutic group: Anti-epileptics, other anti-epileptics ATC code: N03AX12

Gabapentin

Action is potentially via binding to the alpha 2 delta subunits of voltage gated calcium channels and inhibition of glutamide release pre-synaptically and post-synaptically in the CNS. It also stabilizes the nerve membrane by inhibiting calcium ion channel, therefore minimizing abnormal synthesis / firing of impulses.

Methylcobalamin

Methylcobalamin is the neurologically active form of vitamin B12, which increases mylein sheath formation and regenerates neurons and prevents progressive nerve damage.

PHARMACOKINETICS

Gabapentin:

Following oral administration, peak plasma gabapentin concentrations are observed within 2 to 3 hours. Absolute bioavailability of 300 mg gabapentin tablets is approximately 55%. Food has no effect on gabapentin

pharmacokinetics. Gabapentin elimination parameters are independent of dose. However, the extent of gabapentin absorption decreases with increasing dose. Following doses of 300 and 600 mg, absolute bioavailability is 57% and 42% respectively. In normal volunteers the elimination half-life of gabapentin is independent of dose and averages 5 to 7 hours.

Gabapentin is not bound to plasma proteins and has an apparent volume of distribution of 57.7 liters. In patients with epilepsy, gabapentin concentrations in CSF ranged from 7-35% of corresponding steady state trough plasma concentrations. Gabapentin is eliminated solely by renal excretion. Gabapentin does not incude hepatic mixed-function oxidase enzymes responsible for drug metabolism. In elderly patients, age-related alterations in renal function decrease gabapentin plasma clearance and increase gabapentin elimination half-life. Gabapentin elimination-rate constant, plasma clearance, and renal clearance are directly proportional to creatinine clearance. Gabapentin is removed from plasma by haemodialysis.

Methylcobalamin:

In a four-month, double-blind, placebo-controlled trial of type 1 and 2 diabetics with neuropathy, 21 subjects were given oral methylcobalamin at a dose of 500 mcg three times daily, while 22 subjects received placebo. Significant improvements were reported for somatic and autonomic symptoms in the treatment group compared to placebo.

Diabetic Neuropathy: Oral administration of methylcobalamin (500 mcg three times daily for four months) resulted in subjective improvement in burning sensations, numbness, loss of sensation, and muscle cramps. An improvement in reflexes, vibration sense, lower motor neuron weakness, and sensitivity to pain was also observed.

Single-dose administration: When methylcobalamin was administered orally to healthy adult male volunteers at a single dose of 120 mcg and 1500 mcg, the peak serum total vitamin B12 (abbreviated to B12) concentration was reached 3 hr for both doses, and this was dose-dependently. The half-life, increment in the serum total B12 concentration and ΔAUC^{12}_{0} by 12 hr after administration were shown in the following table. 40 to 80 percent of the cumulative amount

of total B12 excreted in the urine by 24hr after administration was excreted within the first 8 hrs.

Dose	^{t}max (hr)	^{C}max (pg/mL)	$^{\Delta C}$max (pg/mL)	$^{\Delta C}$max (%)	ΔAUC^{12}_{0} (pg.hr/mL)	$t_{1/2}$ (hr)
120 µg 1500 µg	2.8 ± 0.2 3.6 ± 0.5	743 ± 47 972 ± 55	37 ± 15 255 ± 51	54 ± 24 36.0 ± 7.9	168 ± 58 2033 ± 510	N.A 12.5

Repeated-dose administration: Methylcobalamin was administered orally to healthy adult male volunteers at dose of 1500 mcg daily for consecutive 12 weeks and changes in the serum total vitamin B12 concentration were determined until 4 weeks after the last administration. The serum concentration increased for the first 4 weeks after administration, reaching about twice as high as the initial value. Thereafter, there was a gradual increase which reached a peak of about 2.8 times the initial value at the 12th week of dosing. The serum concentration declined after the last administration (12 weeks), but was still about 1.8 times the initial value 4 weeks after the last administration.

Clinical efficacy

Methylcobalamin was administered orally to patients with peripheral neuropathies at doses of 1500 mcg and 120 mcg (low dose group) daily divided into three doses for 4 consecutive weeks in a double-blind clinical trial. In the chronic stage and fixed stage in peripheral neuropathies, the improvement rate for moderately to remarkably improved, was 17.6% (6/34) ub 1500 mcg group and 9.7% (3/31) in 120 mcg group. The improvement rate for fairly to remarkably improved, was 64.7% (22/34) in 1500 mcg group and 41.9% (13/31) in 120 mcg group. The dose of 1500 mcg /day was thus demonstrated to be useful.

In a placebo-controlled double-blind clinical trial, Methylcobalamin and cobamamide were administered orally to patients with peripheral neuropathies at doses of 1500 mcg daily for 4 consecutive weeks. The improvement rate for moderately to remarkably improved, in peripheral neuropathies was 38.6% (17/44) in Methylcobalamin, 22.2% (10/45) for cobamamide and 26.7% (12/45) for placebo. Methylcobalamin was thus demonstrated to be useful.

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 tumors 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 tumors in male rats are low-grade malignancies, did not affect survival, did not metastasize or invade surrounding tissue, and were similar to those seen in concurrent controls. The relevance of these pancreatic acinar cell tumors 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/m^2 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.

No effects were observed in pregnant mice given 500 mg/kg/day (approximately 1/2 of the daily human dose on a mg/m^2basis).

An increased incidence of hydroureter and/or hydronephrosis was observed in rats given 2000 mg/kg/day in a fertility and general reproduction study, 1500 mg/kg/day in a teratology study, and 500, 1000, and 2000 mg/kg/day in a perinatal and postnatal study. The significance of these findings is unknown, but they have been associated with delayed development. These doses are also approximately 1 to 5 times the human dose of 3600 mg on a mg/m2 basis.

In a teratology study in rabbits, an increased incidence of post-implantation fetal loss, occurred in doses given 60, 300, and 1500 mg/kg/day during organogenesis. These doses are approximately 1/4 to 8 times the daily human dose of 3600 mg on a mg/m2 basis.

Methylcobalamin is the neurologically active form of vitamin B12. Vitamin B12 comes in several kinds including hydroxy, cyano, and adenosyl, but only the methyl and adenosyl forms are active within the body. Methylcobalamin donates methyl groups to the myelin sheath that insulates nerve fibres and regenerates damaged neurons. In a B12 deficiency, toxic fatty acids destroy the myelin sheath but high enough doses of B12 can repair it. Animal studies have shown that high doses of Methylcobalamin are effective in neuron regeneration and that there is no known toxicity at these doses.

It has been demonstrated by recent studies that combination of Gabapentin and Methylcobalamin shows significantly better symptoms relief with the modest improvement of nervous system, chronic pain, perioperative pain, migraine and enhances immune system function.

Pharmaceutical Particulars

List of ingredients

S. No	Ingredients	Specification
1	Microcrystalline Cellulose	BP
2	Maize Starch	BP
3	PVPK-30 (Povidone)	BP
4	Ethylcellulose	BP
5	Maize Starch (for paste)	BP
6	Purified Talc	BP
7	Croscarmellose Sodium	BP
8	Magnesium Stearate	BP
Film Coating Ingredients		

9	Hydroxypropylmethylcellulose (E15)	BP
10	Purified Talc	BP
11	Titanium Dioxide	BP
12	Polyethylene Glycol 6000	BP
13	Sunset Yellow lake	In House
14	Isopropyl Alcohol	BP
15	Dichloromethane	BP

Incompatibilities

Not Applicable

Shelf life

24 Months from the date of manufacturing

Special precautions for storage

Store at temperature below 30°C, Keep all medicines out of reach of children

Nature and contents of container

Packs of an ALU-ALU blister of 10 Tablets and such 10 blisters in a carton

Special precautions for disposal

No special requirement

Marketing Authorization Holder:

Name : PULSE PHARMACEUTICALS PVT., LTD

Address: Kh.No. 400,407,409, Karondi, Roorkee, Uttarakhand, India

Marketing Authorization Number (s): VN-16237-13

Manufacturer Name: PULSE PHARMACEUTICALS PVT., LTD

Address: Kh.No.400,407,409, Karondi, Roorkee, Uttarakhand, India

Date of first authorization/renewal of the authorization:

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Date of revision of the text:

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