Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT:

GABAMED- M

(Pregabalin and Methylcobalamin Capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Hard gelatin capsule contains:

Pregabalin B.P.……..75 mg

Methylcobalamin U.S.P……1500 mcg

Excipients of known effect;

Each hard gelatin capsule contains lactose monohydrate…..93.50 mg**.**

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pregabalin and Methylcobalamin Capsules are prescribed for the treatment of

- Possesses anxiolytic, analgesic and anticonvulsant activity.
- Possess high bioavailability (90% vs 33-66%) compared to gabapentin.

- Highly effective in relieving the neuropathic pain.
- Improves mood and reduces sleep disturbance.
- Acts as neuroprotective, promotes myelination in neurons.
- Relieves burning sensation, numbness, and loss of sensation & muscle cramps in diabetic neuropathy.
- Peripheral Neuropathy.
- Diabetic Neuropathy.
- Drug Induced Neuropathy

4.2 Posology and method of administration

For adults one capsule two or three times daily or as directed by physician Pregabalin and Methylcobalamin Capsules should be taken before food intake.

4.3 Contraindications

Hypersensitivity. Pregnancy, lactation. Driving or working with machines, or do other dangerous activities

4.4 Special warnings and precautions for use

- May cause peripheral oedema.
- Regular vision check is recommended.
- May decrease platelet count and prolong PR interval.
- Discontinue treatment if patients develop severe angioedema.
- Withdraw treatment gradually over at least 1 week.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent use with oxycodone, lorazepam and ethanol may increase the CNS effects.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

As the potential risk for humans is unknown, effective contraception must be used in women of child bearing potential.

Pregnancy

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

Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Pregabalin and Methylcobalamin Capsules should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the foetus).

Breast-feeding

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.

Fertility

There are no clinical data on the effects of pregabalin on female fertility.

In a clinical trial to assess the effect of pregabalin on sperm motility, healthy male subjects were exposed to pregabalin at a dose of 600 mg/day. After 3 months of treatment, there were no effects on sperm motility.

Methylcobalamin

Methylcobalamin should not be used for the treatment of megaloblastic anaemia of pregnancy.

4.7 Effects on ability to drive and use machines:

Pregabalin and Methylcobalamin Capsules may have minor or moderate influence on the ability to drive and use machines. It may cause dizziness and somnolence and therefore may influence the ability to drive or use machines. Patients are advised not to drive, operate complex machinery or engage in other potentially hazardous activities until it is known whether this medicinal product affects their ability to perform these activities.

Methylcobalamin: No effect.

4.8 Undesirable effects

The pregabalin clinical programme involved over 8900 patients exposed to pregabalin, of whom over 5600 were in double-blind placebo controlled trials.

The most commonly reported adverse reactions were dizziness and somnolence. Adverse reactions were usually mild to moderate in intensity. In all controlled studies, the discontinuation rate due to adverse reactions was 12% for patients receiving pregabalin and 5% for patients receiving placebo. The most common adverse reactions resulting in discontinuation from pregabalin treatment groups were dizziness and somnolence.

In the table 2 below all adverse reactions, which occurred at an incidence greater than placebo and in more than one patient, are listed by class and frequency (very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to

<1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The adverse reactions listed may also be associated with the underlying disease and/or concomitant medicinal products.

In the treatment of central neuropathic pain due to spinal cord injury the incidence of adverse reactions in general, CNS adverse reactions and especially somnolence was increased (see section 4.4).

Additional reactions reported from post-marketing experience are included in italics in the list below.

Table 2. Pregabalin adverse drug reactions

System Organ Class	**Adverse drug reactions**
Infections and infestations	
Common	Nasopharyngitis
Blood and lymphatic system disorders	
Uncommon	Neutropenia
Immune system disorders	
Uncommon	Hypersensitivity
Rare	Angioedema, allergic reaction
Metabolism and nutrition disorders	
Common	Appetite increased
Uncommon	Anorexia, hypoglycaemia
Psychiatric disorders	
Common	Euphoric mood, confusion, irritability, libido decreased, disorientation, insomnia

Uncommon	Hallucination, panic attack, restlessness, agitation, depression, depressed mood, elevated mood , aggression, mood swings, depersonalisation, word finding difficulty, abnormal dreams, libido
Rare	Disinhibition,
Nervous system disorders	
Very Common	Dizziness, somnolence, headache
Common	Ataxia, coordination abnormal, tremor, dysarthria, amnesia, memory impairment, disturbance in attention, paraesthesia, hypoaesthesia, sedation, balance disorder, lethargy
Uncommon	Syncope, stupor, myoclonus, loss of consciousness, psychomotor hyperactivity, dyskinesia, dizziness postural, intention tremor, nystagmus, cognitive disorder, mental impairment, speech disorder, hyporeflexia, hyperaesthesia, burning sensation, ageusia, *malaise*
Rare	Convulsions , hypokinesia, parosmia, dysgraphia
Eye disorders	
Common	Vision blurred, diplopia
Uncommon	Peripheral vision loss, Visual disturbance, eye swelling, visual field defect, visual acuity reduced, eye pain, asthenopia, photopsia, dry eye,
Rare	Rare
Ear and labyrinth disorders	**Ear and labyrinth disorders**
Common	Common
Uncommon	Uncommon
Cardiac disorders	**Cardiac disorders**
Uncommon	Uncommon
Rare	Rare
Vascular disorders	**Vascular disorders**
Uncommon	Uncommon
Respiratory, thoracic and mediastinal disorders	**Respiratory, thoracic and mediastinal disorders**

Uncommon	Uncommon
Rare	Rare
Not known	Not known
Gastrointestinal disorders	**Gastrointestinal disorders**
Common	Common
Uncommon	Uncommon
Rare	Rare
Skin and subcutaneous tissue disorders	**Skin and subcutaneous tissue disorders**
Uncommon	Uncommon
Rare	Rare
Musculoskeletal and connective tissue disorders	**Musculoskeletal and connective tissue disorders**
Common	Muscle cramp, arthralgia, back pain, pain in limb, cervical spasm
Uncommon	Joint swelling, myalgia , muscle twitching, neck pain, muscle stiffness
Rare	Rhabdomyolysis
Renal and urinary disorders	
Uncommon	Urinary incontinence, dysuria
Rare	Renal failure, oliguria, urinary retention
Reproductive system and breast disorders	
Common	Erectile dysfunction
Uncommon	Ejaculation delayed, sexual dysfunction, dysmenorrhoea, breast pain
Rare	Amenorrhoea, breast discharge, breast enlargement, *gynaecomastia*

General disorders and administration site conditions	
Common	Gait abnormal, feeling drunk, fatigue, oedema peripheral, oedema, fall, feeling abnormal
Uncommon	Generalised oedema,pyrexia, face oedema, chest tightness, pain, thirst, chills, asthenia
Investigations	
Common	Weight increased
Uncommon	Blood creatine phosphokinase increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood glucose increased, platelet count decreased, blood creatinine increased , blood potassium decreased, weight decreased.
Rare	White blood cell count decreased

After discontinuation of short-term and long-term treatment with pregabalin withdrawal symptoms have been observed in some patients. The following reactions have been mentioned: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, convulsions, nervousness, depression, pain, hyperhidrosis and dizziness suggestive of physical dependence. The patient should be informed about this at the start of the treatment.

Concerning discontinuation of long-term treatment of pregabalin, data suggest that the incidence and severity of withdrawal symptoms may be dose-related.

Paediatric population

The pregabalin safety profile observed in five paediatric studies in patients with partial seizures with or without secondary generalisation (12 week efficacy and safety study in patients 4 to 16 years of age, n=295; 14 day efficacy and safety study in patients 1 month to younger than 4 years of age, n=175; pharmacokinetic and tolerability study, n=65; and two 1 year open label follow on safety studies, n=54 and n=431) was similar to that observed in the adult studies of patients with epilepsy. The most common adverse events observed in the 12 week study with pregabalin treatment were somnolence, pyrexia, upper respiratory tract infection, increased appetite, weight increased, and nasopharyngitis. The most common adverse events observed in the 14 day study with pregabalin treatment were somnolence, upper respiratory tract infection, and pyrexia

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

In the post-marketing experience, the most commonly reported adverse reactions observed when pregabalin was taken in overdose included somnolence, confusional state, agitation, and restlessness.

In rare occasions, cases of coma have been reported.

Treatment of pregabalin overdose should include general supportive measures and may include haemodialysis if necessary.

Methylcobalamin

No any serious effect due to overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, other antiepileptics ATC code: N03AX16

The active substance, pregabalin, is a gamma-aminobutyric acid analogue ((S)-3-(aminomethyl)-5- methylhexanoic acid).

Pregabalin is an oral medication that is chemically related to gabapentin (Neurontin, Gabarone). It is used for treating pain caused by neurologic diseases such as post herpetic neuralgia as well as seizures. It also is used for treating fibromyalgia. The mechanism of action of pregabalin is unknown. Pregabalin binds to calcium channels on nerves and may modify the release of neurotransmitters (chemicals that nerves use to communicate with each other). Reducing communication between nerves may contribute to pregabalin's effect on pain and seizures.

Methylcobalamin

Vitamin B12 normally plays a significant role in the metabolism of every cell of the body, especially affecting the DNA synthesis and regulation but also fatty acid synthesis and energy production.[40] However, many (though not

all) of the effects of functions of B12 can be replaced by sufficient quantities of folic acid (vitamin B9), since B12 is used to regenerate folate in the body. Most vitamin B12 deficiency symptoms are actually folate deficiency symptoms, since they include all the effects

of pernicious anemia and megaloblastosis, which are due to poor synthesis of DNA when the body does not have a proper supply of folic acid for the production of thymine.[41] When sufficient folic acid is available, all known B12 related deficiency syndromes normalize, save those narrowly connected with the vitamin B12-dependent enzymes Methylmalonyl Coenzyme A mutase, and 5- methyltetrahydrofolate-homocysteine methyltransferase (MTR), also known as methionine synthase; and the buildup of their respective substrates (methylmalonic acid, MMA) and homocysteine.

5.2 Pharmacokinetic properties

Pregabalin:

Absorption: Pregabalin is rapidly absorbed when administered on an empty stomach, with peak plasma concentrations occurring within one hour. Pregabalin oral bioavailability is estimated to be greater than or equal to 90% and is independent of dose. The rate of pregabalin absorption is decreased when given with food resulting in a decrease in Cmax by approximately 25 to 30% and a delay in Tmax to approximately 2.5 hours. Administration with food, however, has no clinically significant effect on the extent of absorption.

Distribution: Pregabalin has been shown to cross the blood–brain barrier in mice, rats, and monkeys. Pregabalin has been shown to cross the placenta in rats and is present in the milk of lactating rats. In humans, the volume of distribution of pregabalin for an orally administered dose is approximately 0.56 L/kg and is not bound to plasma proteins.

Metabolism: Pregabalin undergoes negligible metabolism in humans. Approximately 98% of the radioactivity recovered in the urine was unchanged pregabalin. The major metabolite is N-methyl pregabalin.

Excretion: Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. Renal clearance of pregabalin is 73 mL/minute

Methylcobalamin:

Methylcobalamin as adenosylcobalamin and hydroxocobalamin. These act as co-enzymes in the trans methylation of homocysteine to methionine; in the isomerisation of methylmalonyl co-enzyme to succinyl co-enzyme and with

folate in several metabolic pathways respectively. Deficiency of Vitamin B12 interferes with haemopoiesis and produces megaloblastic anaemia.

5.3 Preclinical safety data

In conventional safety pharmacology studies in animals, pregabalin was well-tolerated at clinically

relevant doses. In repeated dose toxicity studies in rats and monkeys CNS effects were observed, including hypo activity, hyperactivity and ataxia. An increased incidence of retinal atrophy commonly observed in aged albino rats was seen after long term exposure to pregabalin at exposures≥ 5 times the mean human exposure at the maximum recommended clinical dose.

Pregabalin was not teratogenic in mice, rats or rabbits. Foetal toxicity in rats and rabbits occurred only at exposures sufficiently above human exposure. In prenatal/postnatal toxicity studies, pregabalin induced offspring developmental toxicity in rats at exposures >2 times the maximum recommended human exposure.

Adverse effects on fertility in male and female rats were only observed at exposures sufficiently in excess of therapeutic exposure. Adverse effects on male reproductive organs and sperm parameters were reversible and occurred only at exposures sufficiently in excess of therapeutic exposure or were associated with spontaneous degenerative processes in male reproductive organs in the rat. Therefore the effects were considered of little or no clinical relevance.

Pregabalin is not genotoxic based on results of a battery of in vitro and in vivo tests.

Two-year carcinogenicity studies with pregabalin were conducted in rats and mice. No tumours were observed in rats at exposures up to 24 times the mean human exposure at the maximum recommended clinical dose of 600 mg/day. In mice, no increased incidence of tumour was found at exposures similar to the mean human exposure, but an increased incidence of haemangiosarcoma was observed at higher exposures. The non-genotoxic mechanism of pregabalin-induced tumour formation in mice involves platelet changes and associated endothelial cell proliferation. These platelet changes were not present in rats or in humans based on short term and limited long term clinical data. There is no evidence to suggest an associated risk to humans.

In juvenile rats the types of toxicity do not differ qualitatively from those observed in adult rats. However, juvenile rats are more sensitive. At therapeutic exposures, there was evidence of CNS clinical signs of hyperactivity and bruxism and some changes in growth (transient body

weight gain suppression). Effects on the oestrus cycle were observed at 5-fold the human therapeutic exposure. Reduced acoustic startle response was observed in juvenile rats 1-2 weeks after exposure at >2 times the human therapeutic exposure. Nine weeks after exposure, this effect was no longer observable.

Methylcobalamin

Not available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

SR. NO.	INGREDIENTS	SPECIFICATION
1	Lactose Monohydrate	BP
2	Maize Starch	BP
3	Colloidal Silicon Dioxide (Aerosil)	BP
4	Purified Talc	BP
5	Magnesium Stearate	BP

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months from date of manufacturing.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

10 tablets are packed in one Alu-Alu blister such 3 blister are packed in a carton with insert.

6.6 Special precautions for disposal and other handling

This medicinal product does not require any special storage conditions.

7. MANUFACTURED BY:

BRUSSELS LABORATORIES PVT. LTD.,

33, Changodar Ind. Estate,

Sarkhej –Bavla Road,

Changodar - 382210,

Dist – Ahmedabad, Gujarat, India.

MARKETED BY:

PROMED PHARMACEUTICALS LTD.

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Off Waiyaki Way,

Nairobi, 00200, Kenya

8. Marketing authorization number

H2024/CTD10016/22294

9. Date of first registration

April 2024

10. Date of revision of the text: