For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory Only.

PREGABA M 75

1. Generic Name

Pregabalin & Mecobalamin Capsules I.P.

2. Qualitative and quantitative composition

Each hard gelatin capsule contains:

Pregabalin I.P. ……75mg

Mecobalamin I.P. ……...750mcg

Excipients……q.s.

Approved colours used in capsule shell.

Appropriate overages are added to compensate loss on storage.

The excipients used are Talc, Magnesium Stearate, Lactose and Colloidal Silicon Dioxide.

3. Dosage form and strength

Dosage form: Capsules

Strength: Pregabalin – 75mg & Mecobalamin – 750mcg

4. Clinical particulars

4.1 Therapeutic indication

It is indicated for the treatment of adult patients with peripheral neuropathy.

4.2 Posology and method of administration

Posology

As Directed by the physician.

Discontinuation of pregabalin

In accordance with current clinical practice, if pregabalin has to be discontinued, it is recommended this should be done gradually over a minimum of 1 week independent of the indication

Renal impairment

Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. As pregabalin clearance is directly proportional to creatinine clearance, dose reduction in patients with compromised renal function must be individualised according to creatinine clearance (CLcr), determined using the following formula:

$$CL_{cr}(ml/min) = \left[\frac{1.23 \times [140 - age\,(years)] \times weight\,(kg)}{serum\ creatinine\ (\mu mol/l)} \right] (\times\ 0.85 \text{ for female patients})$$

Hepatic impairment

No dose adjustment is required for patients with hepatic impairment.

Paediatric population

The safety and efficacy of PREGABA M 75 in children below the age of 12 years and in adolescents (12-17 years of age) have not been established.

Elderly

Elderly patients may require a dose reduction of pregabalin due to a decreased renal function.

Method of administration

PREGABA M 75 is for oral use only.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients.

4.4 Special warnings and precautions for use

Pregabalin

Diabetic patients

In accordance with current clinical practice, some diabetic patients who gain weight on pregabalin treatment may need to adjust hypoglycemic medicinal products.

Hypersensitivity reactions

There have been reports in the post marketing experience of hypersensitivity reactions, including cases of angioedema. Pregabalin should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper airway swelling occur.

Dizziness, somnolence, loss of consciousness, confusion and mental impairment

Pregabalin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in the elderly population. There have also been post marketing reports of loss of consciousness, confusion and mental impairment. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medicinal product.

Vision-related effects

In controlled trials, a higher proportion of patients treated with pregabalin reported blurred vision than did patients treated with placebo which resolved in a majority of cases with continued dosing. In the clinical studies where ophthalmologic testing was conducted, the incidence of visual acuity reduction and visual field changes was greater in pregabalin-treated patients than in placebo-treated patients; the incidence of fundoscopic changes was greater in placebo-treated patients.

In the post marketing experience, visual adverse reactions have also been reported, including loss of vision, visual blurring or other changes of visual acuity, many of which were transient. Discontinuation of pregabalin may result in resolution or improvement of these visual symptoms.

Renal failure

Cases of renal failure have been reported and in some cases discontinuation of pregabalin did show reversibility of this adverse reaction.

Withdrawal of concomitant anti-epileptic medicinal products

There are insufficient data for the withdrawal of concomitant anti-epileptic medicinal products, once seizure control with pregabalin in the add-on situation has been reached, in order to reach monotherapy on pregabalin.

Withdrawal symptoms

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

Convulsions, including status epilepticus and grand mal convulsions, may occur during pregabalin use or shortly after discontinuing pregabalin.

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

Congestive heart failure

There have been post marketing reports of congestive heart failure in some patients receiving pregabalin. These reactions are mostly seen in elderly cardiovascular compromised patients during pregabalin treatment for a neuropathic indication. Pregabalin should be used with caution in these patients. Discontinuation of pregabalin may resolve the reaction.

Treatment of central neuropathic pain due to spinal cord injury

In the treatment of central neuropathic pain due to spinal cord injury the incidence of adverse reactions in general, central nervous system adverse reactions and especially somnolence was increased. This may be attributed to an additive effect due to concomitant medicinal products (e.g. anti-spasticity agents) needed for this condition. This should be considered when prescribing pregabalin in this condition.

Suicidal ideation and behaviour

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomized placebo controlled studies of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for pregabalin.

Therefore, patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Reduced lower gastrointestinal tract function

There are post marketing reports of events related to reduced lower gastrointestinal tract function (e.g. intestinal obstruction, paralytic ileus, constipation) when pregabalin was co-administered with medications that have the potential to produce constipation, such as opioid analgesics. When pregabalin and opioids will be used in combination, measures to prevent constipation may be considered (especially in female patients and elderly).

Concomitant use with opioids

Caution is advised when prescribing pregabalin concomitantly with opioids due to risk of CNS depression. In a case control study of opioid users, those patients who took pregabalin

concomitantly with an opioid had an increased risk for opioid-related death compared to opioid use alone. This increased risk was observed at low doses of pregabalin (≤ 300 mg, adjusted odds ratio 1.52 [95% CI, 1.04 - 2.22]) and there was a trend for a greater risk at high doses of pregabalin (> 300 mg, adjusted odds ratio 2.51 [95% CI 1.24 - 5.06]).

Misuse, abuse potential or dependence

Cases of misuse, abuse and dependence have been reported. Caution should be exercised in patients with a history of substance abuse and the patient should be monitored for symptoms of pregabalin misuse, abuse or dependence (development of tolerance, dose escalation, drug-seeking behaviour have been reported).

Encephalopathy

Cases of encephalopathy have been reported, mostly in patients with underlying conditions that may precipitate encephalopathy.

Methylcobalamin

Should be given with caution in patients suffering from folate deficiency.

The following warnings and precautions suggested with parent form – vitamin B12

The treatment of vitamin B12 deficiency can unmask the symptoms of polycythemia Vera. Megaloblastic anemia is sometimes corrected by treatment with vitamin B12. But this can have very serious side effects. Don't attempt vitamin B12 therapy without close supervision by your healthcare provider.

Do not take vitamin B12 if Leber's disease, a hereditary eye disease. It can seriously harm the optic nerve, which might lead to blindness.

4.5 Drug-interaction

Pregabalin

Since pregabalin is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (< 2% of a dose recovered in urine as metabolites), does not inhibit drug metabolism *in vitro*, and is not bound to plasma proteins, it is unlikely to produce, or be subject to, pharmacokinetic interactions.

In vivo studies and population pharmacokinetic analysis

Accordingly, in *in vivo* studies no clinically relevant pharmacokinetic interactions were observed between pregabalin and phenytoin, carbamazepine, valproic acid, lamotrigine, gabapentin, lorazepam, oxycodone or ethanol. Population pharmacokinetic analysis indicated that oral antidiabetics, diuretics, insulin, phenobarbital, tiagabine and topiramate had no clinically significant effect on pregabalin clearance.

Oral contraceptives, norethisterone and/or ethinyl oestradiol

Co-administration of pregabalin with the oral contraceptives norethisterone and/or ethinyl oestradiol does not influence the steady-state pharmacokinetics of either substance.

Central nervous system influencing medical products

Pregabalin may potentiate the effects of ethanol and lorazepam. In controlled clinical trials, multiple oral doses of pregabalin co-administered with oxycodone, lorazepam, or ethanol did not result in clinically important effects on respiration. In the postmarketing experience, there are reports of respiratory failure and coma in patients taking pregabalin and other central

nervous system (CNS) depressant medicinal products. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone.

Interactions and the elderly

No specific pharmacodynamic interaction studies were conducted in elderly volunteers. Interaction studies have only been performed in adults.

Methylcobalamin

The data are unavailable for Methylcobalamin drug interaction, however evidences for parent drug, vitamin B12 are as follows:

Serum concentrations may be decreased by use of oral contraceptives.

Many of these interactions are unlikely to be of clinical significance but should be taken into account when performing assays for blood concentrations.

Parenteral chloramphenicol may attenuate the effect of vitamin B12 in anaemia.

Folic acid, particularly in large doses, can cover up vitamin B12 deficiency, and cause serious health effects.

Early research suggests that vitamin C supplements can destroy dietary vitamin B12. It isn't known whether this interaction is important, but to stay on the safe side, take vitamin C supplements at least 2 hours after meals.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregabalin

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 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

Pregabalin is excreted into human milk. The effect of pregabalin on newborns/infants is unknown. A decision must be made whether to discontinue breast-feeding or to discontinue pregabalin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

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

In a reported 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.

A fertility study in female rats has shown adverse reproductive effects. Fertility studies in male rats have shown adverse reproductive and developmental effects. The clinical relevance of these findings is unknown.

Methylcobalamin

Vitamin B12 is likely safe for pregnant or breast-feeding women when taken by mouth in the amounts recommended. Don't take larger amounts. The safety of larger amounts is unknown.

4.7 Effects on ability to drive and use machines

It 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.

4.8 Undesirable effects

Pregabalin

The pregabalin clinical programme involved over 8,900 patients exposed to pregabalin, of whom over 5,600 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 below table 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.

Additional reactions reported from postmarketing experience are included in italics in the list below.

Pregabalin Adverse Drug Reactions

System Organ Class	**Adverse drug reactions**
Infections and infestations	
Common	Nasopharyngitis
Blood and lymphatic system disorders	

Uncommon	Neutropaenia
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, disorientation, insomnia, libido decreased
Uncommon	Hallucination, panic attack, restlessness, agitation, depression, depressed mood, elevated mood, *aggression*, mood swings, depersonalisation, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy
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, parosmia, hypokinesia, 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, lacrimation increased, eye irritation
Rare	Vision loss, keratitis, oscillopsia, altered visual depth perception, mydriasis, strabismus, visual brightness
Ear and labyrinth disorders	
Common	Vertigo
Uncommon	Hyperacusis
Cardiac disorders	
Uncommon	Tachycardia, atrioventricular block first degree, sinus bradycardia, congestive heart failure
Rare	QT prolongation, sinus tachycardia, sinus arrhythmia
Vascular disorders	
Uncommon	Hypotension, hypertension, hot flushes, flushing, peripheral coldness
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness
Rare	Pulmonary oedema, throat tightness
Gastrointestinal disorders	
Common	Vomiting, nausea, constipation, diarrhoea, flatulence, abdominal distension, dry mouth
Uncommon	Gastroesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral
Rare	Ascites, pancreatitis, swollen tongue, dysphagia
Skin and subcutaneous tissue disorders	
Uncommon	Rash papular, urticaria, hyperhidrosis, pruritus

Rare	Stevens Johnson syndrome, cold sweat
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	Sexual dysfunction, ejaculation delayed, dysmenorrhoea, breast pain
Rare	Amenorrhoea, breast discharge, breast enlargement, gynaecomastia
General disorders and administration site conditions	
Common	Oedema peripheral, oedema, gait abnormal, fall, feeling drunk, feeling abnormal, fatigue
Uncommon	Generalised oedema, face oedema, chest tightness, pain, pyrexia, 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.

Methylcobalamin

Methylcobalamin is relatively safe and devoid of side effects. However, it could infrequently cause the following reactions.

Cardiovascular: pulmonary edema and congestive heart failure early in treatment; peripheral vascular thrombosis.

Hematological: polycythemia Vera

Gastrointestinal: mild transient diarrhea

Dermatological: itching; transitory exanthema

Miscellaneous: feeling of swelling of entire body and serious allergic reactions

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting. By reporting side effects, you can help provide more information on the safety of this medicine

4.9 Overdose

Pregabalin

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. Seizures were also reported. 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

Toxicity due to overdosage with Methylcobalamin is not known.

5. Pharmacological properties

5.1 Mechanism of Action

Pregabalin

Pregabalin binds to an auxiliary subunit (α_2-δ protein) of voltage-gated calcium channels in the central nervous system.

Methylcobalamin

Methylcobalamin (Methyl-B12) is one of the two forms of biologically active vitamin B12. Methyl-B12 is the principal form of circulating vitamin B12, hence the form which is transported into peripheral tissue. Methyl-B12 is absorbed by the intestine by a specific mechanism which uses the intrinsic factor and by a diffusion process in which approximately

1% of the ingested dose is absorbed. Cyanocobalamin and hydroxycobalamin are forms of the vitamin that require conversion to methylcobalamin. Both vitamin B12 and folic acid are required for synthesis of deoxyribonucleic acid (DNA). Folic acid exists as methyl folate in body. A vitamin B12 - containing enzyme removes a methyl group from the latter thereby converting methyl folate to tetrahydrofolic acid (THFA). It is THFA that is involved in DNA synthesis.Methylcobalamin is involved in the synthesis of thymidine from deoxyuridine and promotes the synthesis of DNA and RNA by acting as a coenzyme in the formation of methionine from homocysteine. It enhances synthesis of lecithin, a major component of myelin sheath. Methylcobalamin is known to be extensively taken up by the nerve cell organelles than cyanocobalamin in animals. Methylcobalamin has been demonstrated by neuropathological and electrophysiological studies to inhibit nerve fibre degeneration in neuropathies (in rats and rabbits) induced by drugs, such as adriamycin, acrylamide and vincrinstine or with streptozocin-induced diabetes. Methylcobalamin is also reported to be as effective as steroids in accelerating the recovery of injured nerve tissues from paralysis.

5.2 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-epileptics, other anti-epileptics ATC code: N03AX16

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

Clinical efficacy and safety

Neuropathic pain

Efficacy has been shown in trials in diabetic neuropathy, post herpetic neuralgia and spinal cord injury. Efficacy has not been studied in other models of neuropathic pain.

Pregabalin has been studied in 10 controlled clinical trials of up to 13 weeks with twice a day dosing (BID) and up to 8 weeks with three times a day (TID) dosing. Overall, the safety and efficacy profiles for BID and TID dosing regimens were similar.

In reported clinical trials up to 12 weeks for both peripheral and central neuropathic pain, a reduction in pain was seen by Week 1 and was maintained throughout the treatment period.

In reported controlled clinical trials in peripheral neuropathic pain 35% of the pregabalin treated patients and 18% of the patients on placebo had a 50% improvement in pain score. For patients not experiencing somnolence, such an improvement was observed in 33% of patients treated with pregabalin and 18% of patients on placebo. For patients who experienced somnolence the responder rates were 48% on pregabalin and 16% on placebo.

In reported controlled clinical trial in central neuropathic pain 22% of the pregabalin treated patients and 7% of the patients on placebo had a 50% improvement in pain score.

Epilepsy

Adjunctive Treatment

Pregabalin has been studied in 3 reported controlled clinical trials of 12-week duration with either BID or TID dosing. Overall, the safety and efficacy profiles for BID and TID dosing regimens were similar. A reduction in seizure frequency was observed by Week 1.

Paediatric population

The efficacy and safety of pregabalin as adjunctive treatment for epilepsy in paediatric patients below the age of 12 and adolescents has not been established. The adverse events observed in a pharmacokinetic and tolerability study that enrolled patients from 3 months to 16 years of age (n=65) were similar to those observed in adults. Results of a 1-year open label safety study

in 54 paediatric patients from 3 months to 16 years of age with epilepsy indicate that the adverse events of pyrexia and upper respiratory infections were observed more frequently than in adult studies with epilepsy.

Monotherapy (newly diagnosed patients)

Pregabalin has been studied in 1 controlled clinical trial of 56-week duration with BID dosing. Pregabalin did not achieve non-inferiority to lamotrigine based on the 6-month seizure freedom endpoint. Pregabalin and lamotrigine were similarly safe and well tolerated.

Generalized Anxiety Disorder

Pregabalin has been studied in 6 controlled trials of 4-6 week duration, an elderly study of 8-week duration and a long-term relapse prevention study with a double-blind relapse prevention phase of 6 months duration.

Relief of the symptoms of GAD as reflected by the Hamilton Anxiety Rating Scale (HAM-A) was observed by Week 1.

In reported controlled clinical trials (4-8 week duration) 52% of the pregabalin treated patients and 38% of the patients on placebo had at least a 50% improvement in HAM-A total score from baseline to endpoint.

In reported controlled trials, a higher proportion of patients treated with pregabalin reported blurred vision than did patients treated with placebo which resolved in a majority of cases with continued dosing. Ophthalmologic testing (including visual acuity testing, formal visual field testing and dilated fundoscopic examination) was conducted in over 3600 patients within controlled clinical trials. In these patients, visual acuity was reduced in 6.5% of patients treated with pregabalin, and 4.8% of placebo-treated patients. Visual field changes were detected in 12.4% of pregabalin-treated, and 11.7% of placebo-treated patients. Fundoscopic changes were observed in 1.7% of pregabalin-treated and 2.1% of placebo-treated patients.

Methylcobalamin

Synthesis of the myelin coating of peripheral nerves requires adequate availability of vitamin B12. Myelin is a lipoprotein and methylcobalamin participates in the synthesis of both lipid (a phospholipid/ lipid) and the protein components.

Lipid synthesis: Methylcobalamin supplies necessary methyl group necessary for phospholipid (also referred to as lecithin, the main constituent of medullary sheath lipids) manufacturing.

Protein synthesis: Methylcobalamin also upregulates gene transcription resulting in protein synthesis stimulation.

Even in Wallerian degeneration, wherein the nerve is crushed, methylcobalamin has ability regenerate it and improve conduction. Supplementing the active form of vitamin B12, namely methylcobalamin, is always advantageous since it ensures adequate direct availability of vitamin B12 without depending on the body for conversion from cyanocobalamin (a form of vitamin B12 usually taken) to methylcobalamin.

5.3 Pharmacokinetic properties

Pregabalin

Pregabalin steady-state pharmacokinetics are similar in healthy volunteers, patients with epilepsy receiving anti-epileptic drugs and patients with chronic pain.

Absorption

Pregabalin is rapidly absorbed when administered in the fasted state, with peak plasma concentrations occurring within 1 hour following both single and multiple dose administration. Pregabalin oral bioavailability is estimated to be ≥ 90% and is independent of dose. 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} by approximately 25-30% and a delay in t_{max} to approximately 2.5 hours. However, administration of pregabalin with food has no clinically significant effect on the extent of pregabalin absorption.

Distribution

In preclinical studies, 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 apparent volume of distribution of pregabalin following oral administration is approximately 0.56 l/kg. Pregabalin is not bound to plasma proteins.

Biotransformation

Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabelled pregabalin, approximately 98% of the radioactivity recovered in the urine was 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, there was no indication of racemization of pregabalin S-enantiomer to the R-enantiomer.

Elimination

Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. Pregabalin mean elimination half-life is 6.3 hours. Pregabalin plasma clearance and renal clearance are directly proportional to creatinine clearance. Dose adjustment in patients with reduced renal function or undergoing haemodialysis is necessary.

Linearity/non-linearity

Pregabalin pharmacokinetics are linear over the recommended daily dose range. Inter-subject pharmacokinetic variability for pregabalin is low (< 20%). Multiple dose pharmacokinetics are predictable from single-dose data. Therefore, there is no need for routine monitoring of plasma concentrations of pregabalin.

Gender

Clinical trials indicate that gender does not have a clinically significant influence on the plasma concentrations of pregabalin.

Renal impairment

Pregabalin clearance is directly proportional to creatinine clearance. In addition, pregabalin is effectively removed from plasma by haemodialysis (following a 4 hour haemodialysis treatment plasma pregabalin concentrations are reduced by approximately 50%). Because renal elimination is the major elimination pathway, dose reduction in patients with renal impairment and dose supplementation following haemodialysis is necessary.

Hepatic impairment

No specific pharmacokinetic studies were carried out in patients with impaired liver function. Since pregabalin does not undergo significant metabolism and is excreted predominantly as unchanged drug in the urine, impaired liver function would not be expected to significantly alter pregabalin plasma concentrations.

Paediatric population

Pregabalin pharmacokinetics were evaluated in paediatric patients with epilepsy (age groups: 1 to 23 months, 2 to 6 years, 7 to 11 years and 12 to 16 years) at dose levels of 2.5, 5, 10 and 15 mg/kg/day in a pharmacokinetic and tolerability study.

After oral administration of pregabalin in paediatric patients in the fasted state, in general, time to reach peak plasma concentration was similar across the entire age group and occurred 0.5 hours to 2 hours postdose.

Pregabalin C_{max} and AUC parameters increased in a linear manner with increasing dose within each age group. The AUC was lower by 30% in paediatric patients below a weight of 30 kg due to an increased body weight adjusted clearance of 43% for these patients in comparison to patients weighing ≥30 kg.

Pregabalin terminal half-life averaged about 3 to 4 hours in paediatric patients up to 6 years of age, and 4 to 6 hours in those 7 years of age and older.

Population pharmacokinetic analysis showed that creatinine clearance was a significant covariate of pregabalin oral clearance, body weight was a significant covariate of pregabalin apparent oral volume of distribution, and these relationships were similar in paediatric and adult patients.

Pregabalin pharmacokinetics in patients younger than 3 months old have not been studied.

Elderly

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

Breast-feeding mothers

The pharmacokinetics of 150 mg pregabalin given every 12 hours (300 mg daily dose) was evaluated in 10 lactating women who were at least 12 weeks postpartum. Lactation had little to no influence on pregabalin pharmacokinetics. Pregabalin was excreted into breast milk with average steady-state concentrations approximately 76% of those in maternal plasma. The estimated infant dose from breast milk (assuming mean milk consumption of 150 ml/kg/day) of women receiving 300 mg/day or the maximum dose of 600 mg/day would be 0.31 or 0.62 mg/kg/day, respectively. These estimated doses are approximately 7% of the total daily maternal dose on a mg/kg basis.

METHYLCOBALAMIN ABSORPTION & PLASMA LEVELS

Methylcobalamin and cyanocobalamin are similarly absorbed from the gastrointestinal (GI) tract. The cobalamins are bound to specialized transport proteins - intrinsic factor (of stomach), which facilitates their entry into the cells lining the intestinal mucosa. Entry in physiological conditions occur only via the ileum. Inside the body, mecobalamin is transported into all other cells only when bound to another transport protein, transcobalamin II. The Cmax of B12 is reached in 3 hours. Following single dose intake of 1500 mcg, the C_{max} obtained is 972 pg/ml.

Fat

In the liver significantly more cobalamin accumulates following methylcobalamin intake than cyanocobalamin. 40-80% of total B12 is excreted in urine in 24 hours. Human methylcobalamin urinary excretion is about one third that of a similar dose of cyanocobalamin, indicating substantial greater tissue retention.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Pregabalin

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 hypoactivity, 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 tumours 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 tumours 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 estrus 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.

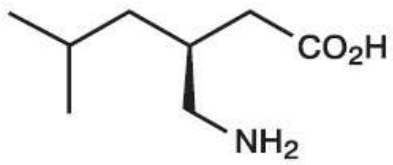
Methylcobalamin

No preclinical data of relevance available.

7. Description

Pregabalin

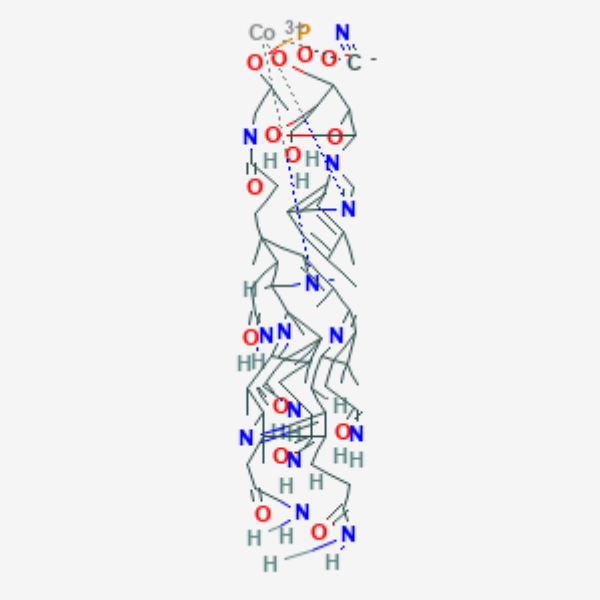
Pregabalin is described chemically as (S)-4-amino-3-(2-methylpropyl) butyric acid. The molecular formula is $C_8H_{17}NO_2$ and the molecular weight is 159.23. The chemical structure of pregabalin is:



Pregabalin is a white to off-white powder which is sparingly soluble in water.

Mecobalamin

It is chemically cobalt(3+);[(2R,5S)-5-(5,6-dimethylbenzimidazol-1-yl)-4-hydroxy-2-(hydroxymethyl)oxolan-3-yl] 1-[3-[(2R,3R,4Z,7S,9Z,12S,13S,14Z,17S,18S,19R)-2,13,18-tris(2-amino-2-oxoethyl)-7,12,17-tris(3-amino-3-oxopropyl)-3,5,8,8,13,15,18,19-octamethyl-2,7,12,17-tetrahydro-1H-corrin-21-id-3-yl]propanoylamino]propan-2-yl phosphate;cyanide and having molecular formula of $C_{63}H_{88}CoN_{14}O_{14}P$ and molecular weight of 1355.4 g/mol and chemical structure is:



Pregabalin and Mecobalamin capsules are orange/black coloured, size "1" capsules, filled with light pink colour granules. The excipients used are Talc, Magnesium Stearate, Lactose and Colloidal Silicon Dioxide.

8. Pharmaceutical particulars

8.1 Incompatibilities

None stated

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

PREGABA M 75 is available in Blister strips of 15 Capsules.

8.4 Storage and handing instructions

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

9. Patient Counselling Information

Package leaflet: Information for the user

PREGABA M 75

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.

- If you have any further questions, ask your doctor or pharmacist.

- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1 What PREGABA M 75 is and what it is used for

PREGABA M 75 contains the active substance Pregabalin and Methylcobalamin.

Pregabalin belongs to a group of medicines used to treat epilepsy, neuropathic pain and Generalised Anxiety Disorder (GAD) in adults. Methylcobalamin homologue of vitamin B12, found in the brain that participates in trans methylation as a B12 containing coenzyme and plays a fundamental role in protein synthesis and stimulates methionine synthesis from homocysteine and helps to restore normal levels of DNA and RNAs in nerve cells. It also enhances the formation of lecithin (another major component of the myelin sheath).

Peripheral and central neuropathic pain: PREGABA M 75 is indicated for the treatment of adult patients with peripheral neuropathy.

9.2 What you need to know before you take PREGABA M 75

Do not take PREGABA M 75:

If you are allergic to pregabalin, methylcobalamin or any of the other ingredients of this medicine.

Warnings and Precautions

Talk to your doctor or pharmacist before taking PREGABA M 75

• Some patients taking PREGABA M 75 have reported symptoms suggesting an allergic reaction. These symptoms include swelling of the face, lips, tongue, and throat, as well as diffuse skin rash. Should you experience any of these reactions, you should contact your physician immediately.

• PREGABA M 75 has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in elderly patients. Therefore, you should be careful until you are used to any effect the medicine might have.

• PREGABA M 75 may cause blurring or loss of vision, or other changes in eyesight, many of which are temporary. You should immediately tell your doctor if you experience any changes in your vision.

• Some patients with diabetes who gain weight while taking PREGABA M 75 may need an alteration in their diabetic medicines.

• Certain side effects may be more common, such as sleepiness, because patients with spinal cord injury may be taking other medicines to treat, for example, pain or spasticity, that have similar side effects to PREGABA M 75 and the severity of these effects may be increased when taken together.

• There have been reports of heart failure in some patients when taking PREGABA M 75; these patients were mostly elderly with cardiovascular conditions. Before taking this medicine you should tell your doctor if you have a history of heart disease.

• There have been reports of kidney failure in some patients when taking PREGABA M 75. If while taking PREGABA M 75 you notice decreased urination, you should tell your doctor as stopping the medicine may improve this.

• A small number of people being treated with anti-epileptics such as PREGABA M 75 have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.

• When PREGABA M 75 is taken with other medicines that may cause constipation (such as some types of pain medicines) it is possible that gastrointestinal problems may occur (e.g. constipation, blocked or paralysed bowel). Tell your doctor if you experience constipation, especially if you are prone to this problem.

• Before taking this medicine you should tell your doctor if you have a history of alcoholism or any drug abuse or dependence. Do not take more medicine than prescribed.

• There have been reports of convulsions when taking PREGABA M 75 or shortly after stopping PREGABA M 75. If you experience a convulsion, contact your doctor immediately.

• There have been reports of reduction in brain function (encephalopathy) in some patients taking drug when they have other conditions. Tell your doctor if you have a history of any serious medical conditions, including liver or kidney disease.

• Should be given with caution in patients suffering from folate deficiency.

• Don’t attempt PREGABA M 75 without close supervision by your healthcare provider because the treatment of vitamin B12 deficiency can unmask the symptoms of polycythemia Vera.

• Do not take PREGABA M 75 if Leber's disease, a hereditary eye disease. It can seriously harm the optic nerve, which might lead to blindness.

Children and adolescents

The safety and efficacy in children and adolescents (under 18 years of age) has not been established and therefore, PREGABA M 75 should not be used in this age group.

Other medicines and PREGABA M 75

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

PREGABA M 75 and certain other medicines may influence each other (interaction). When taken with certain other medicines, PREGABA M 75 may potentiate the side effects seen with these medicines, including respiratory failure and coma. The degree of dizziness, sleepiness and decreased concentration may be increased if PREGABA M 75 is taken together with medicines containing:

Oxycodone – (used as a pain-killer)

Lorazepam – (used for treating anxiety)

Alcohol

Parenteral chloramphenicol may attenuate the effect of PREGABA M 75 in anaemia.

Folic acid, particularly in large doses, can cover up vitamin B12 deficiency, and cause serious health effects. Vitamin C supplements can destroy dietary vitamin B12. It isn't known whether this interaction is important, but to stay on the safe side, take vitamin C supplements at least 2 hours after meals.

PREGABA M 75 with food, drink and alcohol

PREGABA M 75 capsules may be taken with or without food.

It is advised not to drink alcohol while taking PREGABA M 75.

Pregnancy and breast-feeding

PREGABA M 75 should not be taken during pregnancy or when breast-feeding, unless you are told otherwise by your doctor. Effective contraception must be used by women of child-bearing potential. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

PREGABA M 75 may produce dizziness, sleepiness and decreased concentration. You should not drive, operate complex machinery or engage in other potentially hazardous activities until you know whether this medicine affects your ability to perform these activities.

9.3 How to take PREGABA M 75

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. Your doctor will determine what dose is appropriate for you.

PREGABA M 75 is for oral use only.

Peripheral and central neuropathic pain :

• Take the number of capsules as instructed by your doctor.

DOSE: As Directed by physician

If you have the impression that the effect of PREGABA M 75 is too strong or too weak, talk to your doctor or pharmacist. If you are an elderly patient (over 65 years of age), you should take PREGABA M 75 normally except if you have problems with your kidneys.

Your doctor may prescribe a different dosing schedule and/or dose if you have problems with your kidneys. Swallow the capsule whole with water. Continue taking PREGABA M 75 until your doctor tells you to stop.

If you take more PREGABA M 75 than you should

Call your doctor or go to the nearest hospital emergency unit immediately. Take your box or bottle of PREGABA M 75 capsules with you. You may feel sleepy, confused, agitated, or restless as a result of taking more PREGABA M 75 than you should. Fits have also been reported.

If you forget to take PREGABA M 75

It is important to take your PREGABA M 75 capsules regularly at the same time each day. If you forget to take a dose, take it as soon as you remember unless it is time for your next dose. In that case, just carry on with the next dose as normal. Do not take a double dose to make up for a forgotten dose.

If you stop taking PREGABA M 75

Do not stop taking PREGABA M 75 unless your doctor tells you to. If your treatment is stopped it should be done gradually over a minimum of 1 week. After stopping long and short-term PREGABA M 75 treatment, you need to know that you may experience certain side effects. These include, trouble sleeping, headache, nausea, feeling anxious, diarrhoea, flulike symptoms, convulsions, nervousness, depression, pain, sweating, and dizziness. These symptoms may occur more commonly or severely if you have been taking PREGABA M 75 for a longer period of time. If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4 . Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common: may affect more than 1 in 10 people

Dizziness, drowsiness, headache.

Common: may affect up to 1 in 10 people

• Increased appetite.

• Feeling of elation, confusion, disorientation, decrease in sexual interest, irritability.

• Disturbance in attention, clumsiness, memory impairment, loss of memory, tremor, difficulty with speaking, tingling feeling, numbness, sedation, lethargy, insomnia, fatigue, feeling abnormal.

• Blurred vision, double vision.

• Vertigo, problems with balance, fall.

• Dry mouth, constipation, vomiting, flatulence, diarrhoea, nausea, swollen abdomen.

• Difficulties with erection.

• Swelling of the body including extremities.

• Feeling drunk, abnormal style of walking.

• Weight gain.

• Muscle cramp, joint pain, back pain, pain in limb.

• Sore throat.

Uncommon: may affect up to 1 in 100 people

• Loss of appetite, weight loss, low blood sugar, high blood sugar.

• Change in perception of self, restlessness, depression, agitation, mood swings, difficulty finding words, hallucinations, abnormal dreams, panic attack, apathy, aggression, elevated mood, mental impairment, difficulty with thinking, increase in sexual interest, problems with sexual functioning including inability to achieve a sexual climax, delayed ejaculation.

• Changes in eyesight, unusual eye movement, changes in vision including tunnel vision, flashes of light, jerky movements, reduced reflexes, increased activity, dizziness on standing, sensitive skin, loss of taste, burning sensation, tremor on movement, decreased consciousness, loss of consciousness, fainting, increased sensitivity to noise, feeling unwell.

• Dry eyes, eye swelling, eye pain, weak eyes, watery eyes, eye irritation.

• Heart rhythm disturbances, increased heart rate, low blood pressure, high blood pressure, changes in heartbeat, heart failure.

• Flushing, hot flushes.

• Difficulty breathing, dry nose, nasal congestion.

• Increased saliva production, heartburn, numb around mouth.

• Sweating, rash, chills, fever.

• Muscle twitching, joint swelling, muscle stiffness, pain including muscle pain, neck pain.

• Breast pain.

• Difficulty with or painful urination, incontinence.

• Weakness, thirst, chest tightness.

• Changes in blood and liver test results (blood creatinine phosphokinase increased, alanine amino transferase increased, aspartate aminotransferase increased, platelet count decreased, Neutropaenia, increase in blood creatinine, decrease in blood potassium).

• Hypersensitivity, swollen face, itchiness, hives, runny nose, nose bleed, cough, snoring.

• Painful menstrual periods.

• Coldness of hands and feet.

Rare: may affect up to 1 in 1,000 people

• Abnormal sense of smell, swinging vision, altered perception of depth, visual brightness, vision loss.

• Dilated pupils, cross eyes.

• Cold sweat, tightness of the throat, swollen tongue.

• Inflammation of the pancreas.

• Difficulty in swallowing.

• Slow or reduced movement of the body.

• Difficulty with writing properly.

• Increased fluid in the abdomen.

• Fluid in the lungs.

• Convulsions.

• Changes in the recording of electrical changes (ECG) in the heart which correspond to heart rhythm disturbances.

• Muscle damage.

• Breast discharge, abnormal breast growth, breast growth in males.

• Interrupted menstrual periods.

• Kidney failure, reduced urine volume, urinary retention.

• Decrease in white blood cell count.

• Inappropriate behaviour.

• Allergic reactions (which may include difficulty breathing, inflammation of the eyes (keratitis) and a serious skin reaction characterized by rash, blisters, peeling skin and pain).

• Jaundice (yellowing of the skin and eyes).

Very rare: may affect up to 1 in 10,000 people

• Liver failure.

• Hepatitis (inflammation of the liver).

Unknown:

Cardiovascular: pulmonary edema and congestive heart failure early in treatment; peripheral vascular thrombosis.

Hematological: polycythemia Vera

Gastrointestinal: mild transient diarrhea

Dermatological: itching; transitory exanthema

Miscellaneous: feeling of swelling of entire body and serious allergic reactions

If you experience swollen face or tongue or if your skin turns red and starts to blister or peel, you should seek immediate medical advice.

Certain side effects may be more common, such as sleepiness, because patients with spinal cord injury may be taking other medicines to treat, for example, pain or spasticity, that have similar side effects to Pregabalin and the severity of these effects may be increased when taken together. If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting. By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store PREGABA M

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

9.6 Contents of the pack and other information

What PREGABA M contains

The active substances in PREGABA M are Pregabalin and Mecobalamin.

Approved colours used in capsule shell. Appropriate overages are added to compensate loss on storage.

The excipients used are Talc, Magnesium Stearate, Lactose and Colloidal Silicon Dioxide.

10. Details of manufacturer

Manufactured in India by:

Ravenbhel Healthcare Pvt Ltd.

(WHO and cGMP Certified Company)

16-17, EPIP, SIDCO, Kartholi, Bari Brahmana, Jammu – 181133.

11. Details of permission or licence number with date

Mfg Lic No. JK/01/57 issued on 24.05.2018

12. Date of revision

MAY/2020

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/PREGABA M 75 mg/MAY-20/02/PI