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

PREGEB M 75/PREGALIN M 75/PREGABA M 75

1. **Generic Name**

   Pregabalin and Methylcobalamin capsules I.P.

2. **Qualitative and quantitative Composition:**

   PREGALIN M 75/PREGEB M 75/PREGABA M 75

   Each hard gelatin capsule contains:

   Pregabalin I.P. ……75mg

   Methylcobalamin I.P. ……...750 mcg

   Appropriate overage of Methylcobalamin is added to compensate loss on storage.

   Approved colours used in empty hard gelatin capsule shells.

   The excipients used are Talc, Starcaptm Superior Flow Maize Starch.

3. **Dosage form and strength**

   Dosage form: Hard gelatin capsules

   Strength: 75 mg and 750 mcg

4. **Clinical particulars**

4.1. Therapeutic indication

For the treatment of adult patients with peripheral neuropathy.

4.2. Posology and method of administration

Posology

Treatment will be started with a capsule containing pregabalin 150mg with Methylcobalamin 750mcg once daily or a capsule containing pregabalin 75mg with Methylcobalamin 750mcg twice daily. Based on individual patient response and tolerability, the dose may be increased to 300 mg per day after an interval of 3 to 7 days, and if needed, to a maximum dose of four capsules of pregabalin 150mg with Methylcobalamin 750mcg per day in divided doses.

The dose range of pregabalin is 150 to 600 mg per day given in either two or three divided doses. Prior to starting treatment with Pregabalin, a discussion should be held with patients to put in place a strategy for ending treatment with Pregabalin to minimise the risk of dependence, addiction, and drug withdrawal syndrome.

Discontinuation of pregabalin

In accordance with current clinical practice, if pregabalin must 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 (CL_{cr}), as indicated in Table determined using the following formula:

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

Pregabalin is removed effectively from plasma by haemodialysis (50% of drug in 4 hours). For patients receiving haemodialysis, the pregabalin daily dose should be adjusted based on renal function. In addition to the daily dose, a supplementary dose should be given immediately following every 4-hour haemodialysis treatment.

Table: Pregabalin Dose Adjustment Based on Renal Function

Creatinine clearance (CL_{cr}) (mL/min)	**Total pregabalin daily dose***		**Dose regimen**
	Starting dose (mg/day)	Maximum dose (mg/day)	
≥ 60	150	600	BID or TID
≥ 30 - < 60	75	300	BID or TID
≥ 15 - < 30	25-50	150	Once daily or BID
< 15	25	75	Once daily
Supplementary dosage following haemodialysis (mg)			
	25	100	Single dose*

TID = Three divided doses
BID = Two divided doses
* Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose
+ Supplementary dose is a single additional dose.

Hepatic impairment

No dose adjustment is required for patients with hepatic impairment.

Paediatric population

The safety and efficacy of Pregabalin 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

It may be taken with or without food.
It is for oral use only.

4.3. Contraindications

- Hypersensitivity to the active substance 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 hypoglycaemic medicinal products.

Hypersensitivity reactions

There have been reports in the postmarketing 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.

Severe cutaneous adverse reactions (SCARs)

SCARs including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported rarely in association with pregabalin treatment. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, pregabalin should be withdrawn immediately and an alternative treatment considered (as appropriate).

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 postmarketing 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 postmarketing 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.

Congestive heart failure

There have been postmarketing 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.

Respiratory depression

There have been reports of severe respiratory depression in relation to pregabalin use. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment, concomitant use of CNS depressants and the elderly may be at higher risk of experiencing this severe adverse reaction. Dose adjustments may be necessary in these patients.

Reduced lower gastrointestinal tract function

There are postmarketing 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 (adjusted odds ratio [aOR], 1.68 [95% CI, 1.19 – 2.36]). This increased risk was observed at low doses of pregabalin (≤ 300 mg, aOR 1.52 [95% CI, 1.04 – 2.22]) and there was a trend for a greater risk at high doses of pregabalin (> 300 mg, aOR 2.51 [95% CI 1.24 – 5.06]).

Misuse, abuse potential or dependence

Pregabalin can cause drug dependence, which may occur at therapeutic doses. Cases of abuse and misuse have been reported. Patients with a history of substance abuse may be at higher risk for pregabalin misuse, abuse, and dependence, and pregabalin should be used with caution in such patients. Before prescribing pregabalin, the patient's risk of misuse, abuse or dependence should be carefully evaluated.

Patients treated with pregabalin should be monitored for symptoms of pregabalin misuse, abuse, or dependence, such as development of tolerance, dose escalation and drug-seeking behaviour.

Withdrawal symptoms

Prior to starting treatment with pregabalin, a discussion should be held with patients to explain the risk of dependence, addiction, and drug withdrawal syndrome. A withdrawal strategy for ending treatment with pregabalin should also be put in place with the patient before starting treatment (there may be exceptions to this in specific clinical situations such as symptom management in end-of-life palliative care, and for use in epilepsy).

After discontinuation of short-term and long-term treatment with pregabalin, upon abrupt cessation of therapy or dose reduction withdrawal symptoms have been observed. The following symptoms have been reported: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, nervousness, depression, suicidal ideation, pain, convulsion, hyperhidrosis, and dizziness. The occurrence of withdrawal symptoms following discontinuation of pregabalin may indicate drug dependence. The patient should be informed about this at the start of the

treatment. If pregabalin should be discontinued, it is recommended this should be done gradually over a minimum of 1 week independent of the indication.

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.

When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take in excess of weeks or months. Patients should be informed of this when the medication is first prescribed.

The reduction schedule for a patient should be tailored to the individual and should be modified to allow intolerable withdrawal symptoms to improve before making the next reduction. If using a published withdrawal schedule, apply it flexibly to accommodate the person's preferences, changes to their circumstances and the response to dose reductions.

Reduce the dose by a fixed amount at each decrement, unless clinical risk is such that rapid withdrawal is needed.

If a patient develops withdrawal reactions, consider pausing the taper or increasing the dosage to the previous tapered dosage level.

Encephalopathy

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

Women of childbearing potential/Contraception

Pregabalin use in the first trimester of pregnancy may cause major birth defects in the unborn child. Pregabalin should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus. Women of childbearing potential have to use effective contraception during treatment. If women take this drug during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

Drug dependence, tolerance and potential for abuse

Drug addiction comprises behavioural, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use and possible tolerance or physical dependence. Physical dependence is a state that develops because of physiological adaptation in response to repeated drug use, which manifests as withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. Addiction and dependence are related but distinct presentations and in discussing these themes, terminology that apportion blame to the individual should be avoided.

For all patients, prolonged use of this product may lead to drug dependence and addiction but can occur with short-term use at recommended therapeutic doses. The risks are increased in individuals with current or history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).

Additional support and monitoring may be necessary when prescribing for patients at risk of drug misuse.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of symptom control as initially experienced. Patients may also supplement their treatment with additional medications to achieve the same effect. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse, or addiction.

The clinical need for treatment with pregabalin should be reviewed regularly, with frequent assessments of patients being undertaken during their treatment.

Methylcobalamin

It 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 polycythaemia 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 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. Drugs interactions

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.

<u>In vivo studies and population pharmacokinetic analysis</u>

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.

<u>Oral contraceptives, norethisterone and/or ethinyl oestradiol</u>

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

<u>Central nervous system influencing medical products</u>

Pregabalin may potentiate the effects of ethanol and lorazepam. In the postmarketing experience, there are reports of respiratory failure, coma and deaths in patients taking pregabalin and opioids and/or 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.

<u>Interactions and the elderly</u>

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

Methylcobalamin

The data are unavailable for Mecobalamin drug interaction, however evidence for parent drug – vitamin B12 are as follows; Absorption from the gastrointestinal tract may be reduced by neomycin, amino salicylic acid, histamine H2-antagonists, omeprazole, and colchicine. 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 in anaemia. Potassium supplements can reduce absorption of vitamin B12 in some people and might contribute to vitamin B12 deficiency. Folic acid, particularly in large doses, can cover up vitamin B12 deficiency, and cause serious health effects. Be sure that healthcare provider checks vitamin B12 levels before start of folic acid. 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. Heavy drinking for at least a two-week period can decrease vitamin B12 absorption from the gastrointestinal tract.

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

Women of childbearing potential/Contraception

Women of childbearing potential have to use effective contraception during treatment.

Pregnancy

Studies in animals have shown reproductive toxicity.

Pregabalin has been shown to cross the placenta in rats. Pregabalin may cross the human placenta.

Major congenital malformations

Data from a Nordic observational study of more than 2700 pregnancies exposed to pregabalin in the first trimester showed a higher prevalence of major congenital malformations (MCM) among the paediatric population (live or stillborn) exposed to pregabalin compared to the unexposed population (5.9% vs. 4.1%).

The risk of MCM among the paediatric population exposed to pregabalin in the first trimester was slightly higher compared to unexposed population (adjusted prevalence ratio and 95% confidence interval: 1.14 (0.96-1.35)) and compared to population exposed to lamotrigine (1.29 (1.01–1.65)) or to duloxetine (1.39 (1.07–1.82)).

The analyses on specific malformations showed higher risks for malformations of the nervous system, the eye, orofacial clefts, urinary malformations, and genital malformations, but numbers were small and estimates imprecise.

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 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

Pregabalin may have minor or moderate influence on the ability to drive and use machines. Pregabalin 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

None known.

4.8. Undesirable effects

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 table 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.

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

Table Pregabalin Adverse Drug Reaction

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

System Organ Class	Adverse drug reactions
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, depersonalization, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy
Rare	Disinhibition, suicidal behaviour, suicidal ideation.
Not known	Drug dependence
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, parkinsonism
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.

System Organ Class	Adverse drug reactions
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
Not known	Respiratory depression
Gastrointestinal disorders	
Common	Vomiting, nausea, constipation, diarrhoea, flatulence, abdominal distension, dry mouth
Uncommon	Gastrooesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral
Rare	Ascites, pancreatitis, swollen tongue, dysphagia
Hepatobiliary disorders	
Uncommon	Elevated liver enzymes*
Rare	Jaundice
Very rare	Hepatic failure, hepatitis
Skin and subcutaneous tissue disorders	
Uncommon	Rash popular, urticaria, hyperhidrosis, pruritus
Rare	Drug dependence, steven-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, dysmenorrhea, 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

System Organ Class	Adverse drug reactions
Investigations	
Common	Weight increased
Uncommon	Blood creatinine phosphokinase increased, blood glucose increased, platelet count decreased, blood creatinine increased, blood potassium decreased, weight decreased.
Rare	White blood cell count decreased

* Alanine aminotransferase increased (ALT) and aspartate aminotransferase increased (AST).

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.

Psychiatric disorders:

Drug dependence

General disorders and administration site conditions: After discontinuation of short-term and long-term treatment with pregabalin withdrawal symptoms have been observed. The following symptoms have been reported: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, convulsions, nervousness, depression, suicidal ideation, pain, hyperhidrosis, and dizziness. These symptoms may indicate drug 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 adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Report suspected adverse reactions via any point of contact available at www.torrentpharma.com.

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.

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

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 (α2-δ protein) of voltage-gated calcium channels in the central nervous system.

Methylcobalamin

Methylcobalamin is the form of vitamin B12 active in the central nervous system. It is essential for cell growth and replication. In some people the liver may not convert cyanocobalamin, the common supplemental form of vitamin B12, into adequate amounts of Methylcobalamin needed for proper neuronal functioning. Methylcobalamin may exert its neuroprotective effects through enhanced methylation, acceleration of nerve cell growth, or its ability to maintain already healthy homocysteine levels.

5.2. Pharmacodynamic properties

Pregabalin

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 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 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 the 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.

Methylcobalamin

Methylcobalamin is one of the biologically active forms of vitamin B12. It acts as coenzymes in nucleic acid synthesis. It is also closely involved with folic acid in several important metabolic pathways. It (CH3B12) supports the methionine synthetase reaction, which is essential for normal metabolism of folate.

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 Cmax by approximately 25-30% and a delay in tmax 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 racemisation 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 post dose.

Pregabalin Cmax 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

It binds to intrinsic factor; a glycoprotein secreted by the gastric mucosa and is then actively absorbed from the gastrointestinal tract. Absorption is impaired in patients with an absence of intrinsic factor, with a malabsorption syndrome or with disease or abnormality of the gut, or after gastrectomy. Absorption from the gastrointestinal tract can also occur by passive diffusion; little of the vitamin present in food is absorbed in this manner although the process becomes increasingly important with larger amounts such as those used therapeutically. After intranasal dosage, peak plasma concentrations of cyanocobalamin have been reached in 1 to 2 hours. The bioavailability of the intranasal preparation is about 7 to 11% of that by intramuscular injection.

It is extensively bound to specific plasma proteins called trans cobalamins trans cobalamin II appears to be involved in the rapid transport of the cobalamins to tissues. A parent form - vitamin B12 is stored in the liver, excreted in the bile, and undergoes extensive enterohepatic recycling; part of a dose is excreted in the urine, most of it in the first 8 hours; urinary excretion, however, accounts for only a small fraction in the reduction of total body stores acquired by dietary means. Vitamin B12 diffuses across the placenta and appears in breast milk.

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 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.

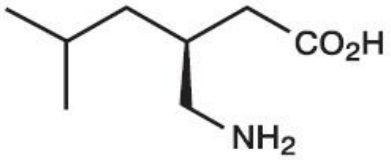
Methylcobalamin

Not Available

7. Description

Pregabalin

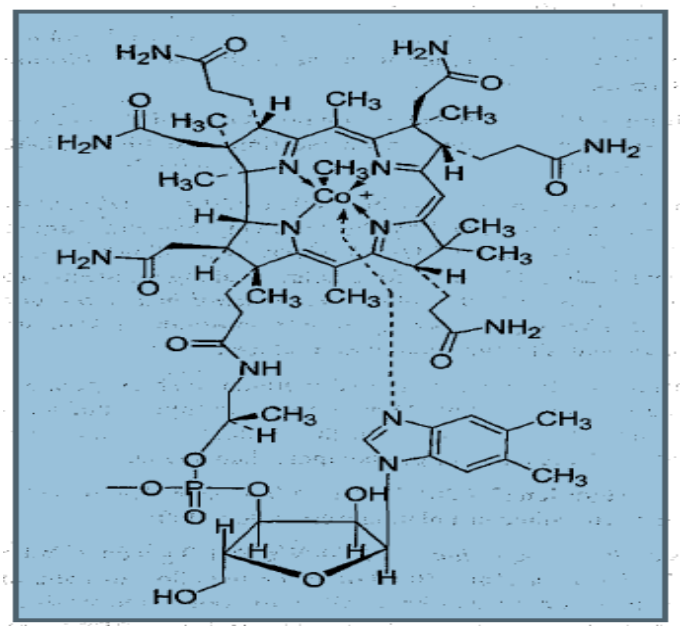
Pregabalin is described chemically as (S)-4-amino-3-(2-methylpropyl) butyric acid. The molecular formula is $C_8H_{17}NO_2$, and the molecular weight is 159.23. The chemical structure of pregabalin is:



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

Mecobalamin

It is chemically Co α-[α-(5,6-dimethyl-1 H-benzoimidazole -1-yl)]-Coβ-methylcobamide and having molecular formula of $C_{63}H_91CoN_{13}O14P$ and molecular Weight of 1344.4 g/mol. and the chemical structure is:



Pregeb M 75 / Pregalin M 75

Hard gelatin size '2', capsules with maroon cap having print "TORRENT" and white body having print torrent logo (Square Emblem Only), filled with pink coloured granular powder.

Pregaba M 75

Hard gelatin "Size 2" capsules with black cap and orange body filled with pink coloured granular powder.

The excipients used are Talc, Starcaptm Superior Flow Maize Starch.

8. Pharmaceutical particulars

8.1. Incompatibilities

Not applicable

8.2. Shelf-life

Do not use later than the date of expiry.

8.3. Packaging information

PREGALIN M 75/PREGEB M 75/PREGABA M 75 is available as blister pack (Alu – PVC / PVDC) of 15 capsules.

8.4. Storage and handing instructions.

Store at a temperature not exceeding 25ºC, protected from light and moisture.

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies.
- Have kidney or liver problems.
- Are pregnant or plan to become pregnant.
- Are breastfeeding or plan to breastfeed.
- Have any serious illness.

- Are taking any medicines (prescription, over the counter, vitamins, or herbal products)

10. Details of manufacturer

Torrent Pharmaceuticals Ltd.

Vill. Bhud & Makhnu Majra,

Teh. Baddi-173 205, Dist. Solan (H.P.), India.

11. Details of permission or licence number with date

MB/05/184 dated on 07.02.2022.

12. Date of revision

JAN-2026

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/PREGEB M 75/PREGALIN M 75/PREGABA M 75/JAN-26/02/PI