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

PREGABA DM/ PREGALIN DM / PREGEB DM 75+20 / 75+30

1. Generic Name

Pregabalin, Methylcobalamin & Duloxetine (Delayed Release) Capsules (75mg + 1500mcg + 20mg & 75mg + 1500 mcg + 30mg).

2. Qualitative and quantitative Composition:

PREGABA DM/ PREGALIN DM / PREGEB DM 75+20 / 75+30

Each Hard Gelatine Capsule Contains:

Pregabalin I.P …….……...….75 mg

(As granules)

Methylcobalamin I.P……..…1500 mcg

(As granules).

Duloxetine Hydrochloride I.P. eq. to Duloxetine……20 mg/30mg

(As delayed release pellets)

Excipients…….q.s.

Colour: Approved Colour used.

PREGABA DM/ PREGALIN DM / PREGEB DM

The excipients used are Lactose, Maize starch and Purified Talc.

3. Dosage form and strength

Dosage form: Delayed Release Hard Gelatine Capsules

Strength: Pregabalin, Methylcobalamin & Duloxetine (75mg + 1500mcg + 20mg & 75mg + 1500 mcg + 30mg).

4. Clinical particulars

4.1. Therapeutic indication

It is indicated for treatment of Patients with Diabetic Peripheral Neuropathic pain and Coexistent Vitamin B12 Deficiency.

4.2. Posology and method of administration

Posology

One capsule once daily, preferably after a meal.

The dose can be adjusted based on therapeutic response and tolerability.

Use in Special Populations

Elderly Patients (≥65 years)

Use with caution; dose adjustment may be required based on renal function and tolerability.

Patients with Renal Impairment

Pregabalin is renally excreted and may require dose reduction in moderate to severe renal impairment (creatinine clearance <60 mL/min).

FDC use is not recommended in patients with severe renal impairment or on dialysis unless individual components are dose-adjusted accordingly.

Patients with Hepatic Impairment

Duloxetine is extensively metabolized in the liver. Use with caution in patients with hepatic impairment.

Contraindicated in severe hepatic impairment (Child-Pugh Class C).

Pediatric Use

Safety and efficacy in patients under 18 years of age have not been established. Not recommended in pediatric population.

Method of administration

Oral use.

4.3. Contraindications

The fixed-dose combination (FDC) of Pregabalin, Methylcobalamin, and Duloxetine is contraindicated in the following conditions:

- Hypersensitivity to any of the active substances (pregabalin, duloxetine, or methylcobalamin) or to any of the excipients in the formulation.
- Patients with a history of angioedema, rhabdomyolysis, or hypersensitivity reactions (e.g., rash, pruritus, urticaria) associated with similar agents.
- Patients with severe renal impairment (creatinine clearance <30 mL/min), including those with chronic kidney disease stages 4 and 5, or those requiring dialysis.
- Patients with severe hepatic impairment or any clinically significant liver disease.
- Uncontrolled hypertension, as this may increase the risk of hypertensive crisis.
- Concomitant use with non-selective, irreversible monoamine oxidase inhibitors (MAOIs) or within 14 days of discontinuing an MAOI.
- Concomitant administration with potent CYP1A2 inhibitors (e.g., fluvoxamine, ciprofloxacin, enoxacin) due to the risk of elevated duloxetine plasma concentrations.
- Patients with a history of major depressive disorder, suicidal ideation, or suicidal behavior.
- Presence of cardiac conduction abnormalities such as atrioventricular (AV) block, chronic heart failure (NYHA Class III–IV), or acute decompensated heart failure.
- History or presence of muscle pain, tenderness, or elevated creatine kinase (CK) levels suggestive of rhabdomyolysis.
- Known diagnosis of chronic obstructive pulmonary disease (COPD) or other significant pulmonary dysfunction.
- Patients experiencing significant fluid retention or peripheral edema (e.g., in the legs, feet, arms, or hands) that may worsen with pregabalin.
- Patients with known or suspected visual disturbances, such as reduced visual acuity, that may be drug-induced.

4.4. Special warnings and precautions for use

Suicidal Ideation and Behaviour

This FDC contains both pregabalin and duloxetine, agents associated with an increased risk of suicidal ideation and behaviour. Patients should be closely monitored during treatment initiation and dose adjustments. Patients and caregivers should be advised to report any changes in mood, behaviour, or emergence of suicidal thoughts immediately.

Central Nervous System Effects

Dizziness, somnolence, confusion, mental impairment, and loss of consciousness may occur with this FDC. These effects may increase the risk of falls and injuries, especially in elderly patients. Until patients are familiar with their individual response, activities requiring mental alertness (e.g. driving, operating machinery) should be avoided.

Risk of Abuse, Misuse, and Dependence

Pregabalin in the FDC has been associated with reports of misuse, abuse, and dependence, particularly in individuals with a history of substance abuse. Patients should be observed for symptoms such as tolerance, dose escalation, or drug-seeking behaviour.

Withdrawal Symptoms

Abrupt discontinuation of this FDC may lead to withdrawal symptoms including insomnia, anxiety, headache, nausea, dizziness, depression, pain, and seizures. Gradual tapering is recommended prior to cessation.

Respiratory Depression

Serious respiratory depression may occur, particularly in elderly patients, those with impaired respiratory function, renal impairment, neurological disorders, or when used concomitantly with opioids or other CNS depressants. Dose adjustment and close monitoring may be necessary.

Visual Disturbances

Blurred vision and other visual abnormalities (e.g. reduced visual acuity, visual field changes) have been reported, primarily related to pregabalin. Most cases resolve on discontinuation. Patients reporting visual symptoms should undergo ophthalmologic evaluation.

Renal Impairment

The FDC is not recommended in patients with severe renal impairment (eGFR <30 mL/min). Dose adjustment may be required in mild to moderate renal dysfunction. Renal function should be monitored periodically.

Hepatic Effects

Duloxetine may cause liver injury and is contraindicated in patients with hepatic impairment. Liver function should be monitored in patients with predisposing hepatic conditions or during long-term use.

Cardiovascular Effects

Pregabalin has been associated with fluid retention and congestive heart failure in predisposed patients, while duloxetine may elevate blood pressure and heart rate. Caution is advised in patients with pre-existing cardiovascular disease. Blood pressure monitoring is recommended during therapy.

Serotonin Syndrome

Serotonin syndrome may occur with duloxetine, particularly when used with other serotonergic or dopamine-modulating agents. Symptoms may include agitation, hallucinations, tachycardia, hyperreflexia, and gastrointestinal symptoms. Treatment should be discontinued immediately if serotonin syndrome is suspected.

Seizures and Mania

Caution is advised in patients with a history of seizures, bipolar disorder, or mania due to risk associated with both pregabalin and duloxetine. Any signs of behavioural changes should be promptly evaluated.

Gastrointestinal Motility Disorders

Use of pregabalin in combination with opioids may increase the risk of reduced lower gastrointestinal motility, including paralytic ileus. Preventive measures may be warranted in high-risk patients (e.g. elderly, females).

Encephalopathy

Cases of encephalopathy have been reported with pregabalin, particularly in patients with predisposing conditions. Clinical suspicion should prompt immediate evaluation and potential discontinuation.

Ophthalmic Effects

Mydriasis has been reported with duloxetine. The FDC should be used with caution in patients with elevated intraocular pressure or at risk of acute narrow-angle glaucoma.

Use in Diabetic Patients

Pregabalin-induced weight gain may require adjustments in hypoglycaemic medications. Glycaemic control should be regularly monitored.

Use in Paediatric Population

This FDC is not recommended for use in children and adolescents below 18 years of age due to limited safety and efficacy data, and increased risk of suicide-related behaviours observed with antidepressants in this population.

Lactose Content

This formulation contains lactose. It should not be used in patients with galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption.

Hypersensitivity Reactions

Hypersensitivity reactions including angioedema have been reported with pregabalin and methylcobalamin. Discontinue immediately if signs such as facial or upper airway swelling occur.

Monitoring Recommendations

- Renal function: Periodically during long-term therapy.
- Liver function: In patients with risk factors or symptoms of hepatic dysfunction.
- Blood pressure and heart rate: Particularly during early treatment phase.
- Mental status: For emergence of suicidality or behavioural changes.
- Visual symptoms: Prompt ophthalmic assessment.

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.

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 the post marketing 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.

Interactions and the elderly

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

Duloxetine:

Monoamine Oxidase Inhibitors (MAOIs):

Due to the risk of serotonin syndrome, duloxetine should not be used in combination with nonselective, irreversible monoamine oxidase inhibitors (MAOIs) or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of duloxetine, at least 5 days should be allowed after stopping Duloxetine before starting an MAOI.

The concomitant use of Duloxetine with selective, reversible MAOIs, like moclobemide, is not recommended. The antibiotic linezolid is a reversible non-selective MAOI and should not be given to patients treated with Duloxetine.

Inhibitors of CYP1A2:

Because CYP1A2 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP1A2 is likely to result in higher concentrations of duloxetine. Fluvoxamine (100 mg once daily), a potent inhibitor of CYP1A2, decreased the apparent plasma clearance of duloxetine by about 77% and increased AUCo-t 6-fold. Therefore, Duloxetine should not be administered in combination with potent inhibitors of CYP1A2 like fluvoxamine.

CNS Medicinal Products:

The risk of using duloxetine in combination with other CNS-active medicinal products has not been systematically evaluated, except in the cases described in this section. Consequently,

caution is advised when Duloxetine is taken in combination with other centrally acting medicinal products or substances, including alcohol and sedative medicinal products (e.g., benzodiazepines, morphinomimetics, antipsychotics, phenobarbital, sedative antihistamines).

Serotonergic agents

In rare cases, serotonin syndrome has been reported in patients using Selective Serotonin Reuptake Inhibitors/Serotonin-Norepinephrine Reuptake Inhibitors (SSRIs/SNRIs) concomitantly with serotonergic agents. Caution is advisable if Duloxetine is used concomitantly with serotonergic agents like SSRIs, SNRIs, tricyclic antidepressants like clomipramine or amitriptyline, MAOIs like moclobemide or linezolid, St John's Wort (Hypericum perforatum) or triptans, tramadol, pethidine, and tryptophan.

Effect of Duloxetine on Other Medicinal Products:

Medicinal products metabolised by CYP1A2:

The pharmacokinetics of theophylline, a CYP1A2 substrate, were not significantly affected by coadministration with duloxetine (60 mg twice daily).

Medicinal products metabolised by CYP2D6:

Duloxetine is a moderate inhibitor of CYP2D6. When duloxetine was administered at a dose of 60 mg twice daily with a single dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold. The co-administration of duloxetine (40 mg twice daily) increases steady-state AUC of tolterodine (2 mg twice daily) by 71% but does not affect the pharmacokinetics of its active 5-hydroxyl metabolite and no dosage adjustment is recommended. Caution is advised if Duloxetine is co-administered with medicinal products that are predominantly metabolised by CYP2D6 (risperidone, tricyclic antidepressants [TCAs], such as nortriptyline, amitriptyline, and imipramine), particularly if they have a narrow therapeutic index (such as flecainide, propafenone, and metoprolol).

Oral contraceptives and other steroidal agents:

Results of in vitro studies demonstrate that duloxetine does not induce the catalytic activity of CYP3A. Specific in vivo drug interaction studies have not been performed.

Anticoagulants and antiplatelet agents:

Caution should be exercised when duloxetine is combined with oral anticoagulants or antiplatelet agents due to a potential increased risk of bleeding attributable to a pharmacodynamic interaction. Furthermore, increases in INR values have been reported when duloxetine was co-administered to patients treated with warfarin. However, concomitant administration of duloxetine with warfarin under steady-state conditions, in healthy volunteers, as part of a clinical pharmacology study, did not result in a clinically significant change in INR from baseline or in the pharmacokinetics of R- or S-warfarin.

Effects of Other Medicinal Products on Duloxetine

Antacids and H2 antagonists: Co-administration of duloxetine with aluminium- and magnesium containing antacids, or duloxetine with famotidine, had no significant effect on the rate or extent of duloxetine absorption after administration of a 40 mg oral dose.

Inducers of CYP1A2: Population pharmacokinetic analyses have shown that smokers have almost 50% lower plasma concentrations of duloxetine compared with non-smokers.

Buprenorphine/opioids medicines: as the risk of serotonin syndrome, a potentially life-threatening condition, is increased.

Methylcobalamin

Absorption of vitamin B12 from the gastrointestinal tract may be reduced by neomycin, aminosalicylic acid, histamine H2-antagonists and colchicine. Serum concentrations may be decreased by concurrent administration 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 in B12 in anemia.

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

PREGNANCY

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 childbearing potential.

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).

Duloxetine

Studies in animals have shown reproductive toxicity at systemic exposure levels (AUC) of duloxetine lower than the maximum clinical exposure.

Two large observational studies do not suggest an overall increased risk of major congenital malformation (one from the US including 2,500 exposed to duloxetine during the first trimester and one from the EU including 1,500 exposed to duloxetine during the first trimester). The analysis on specific malformations such as cardiac malformations show inconclusive results.

In the EU study, maternal exposure to duloxetine during late pregnancy (at any time from 20 weeks gestational age to delivery) was associated with an increased risk for preterm birth (less than 2-fold, corresponding to approximately 6 additional premature births per 100 women treated with duloxetine late in pregnancy). The majority occurred between 35 and 36 weeks of gestation. This association was not seen in the US study.

The US observational data have provided evidence of an increased risk (less than 2-fold) of postpartum haemorrhage following duloxetine exposure within the month prior to birth.

Epidemiological data have suggested that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). Although no studies have investigated the association of PPHN to SNRI treatment, this potential risk cannot be ruled out with duloxetine, taking into account the related mechanism of action (inhibition of the re-uptake of serotonin).

As with other serotonergic medicinal products, discontinuation symptoms may occur in the neonate after maternal duloxetine use near term. Discontinuation symptoms seen with duloxetine may include hypotonia, tremor, jitteriness, feeding difficulty, respiratory distress and seizures. The majority of cases have occurred either at birth or within a few days of birth.

Duloxetine should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus. Women should be advised to notify their physician if they become pregnant, or intend to become pregnant, during therapy.

Methylcobalamin

The usual precautions should be observed when administering drugs during pregnancy, particularly in the first trimester.

However, animal studies are inadequate with respect to effects on pregnancy and/or embryonic/fetal development and/or parturition and/or postnatal development. The potential risk to humans is unknown.

BREASTFEEDING

Pregabalin

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.

Duloxetine

Duloxetine is very weakly excreted into human milk, based on a study of 6 lactating patients who did not breast-feed their children. The estimated daily infant dose on a mg/kg basis is approximately 0.14% of the maternal dose. As the safety of duloxetine in infants is not known, the use of Duloxetine while breast-feeding is not recommended.

Methylcobalamin

There are no data available for Mecobalamin to be used in lactating women. Since vitamin B12 is distributed into breast milk, its use is usually compatible with breast feeding.

FERTILITY

Pregabalin

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.

Duloxetine

In animal studies, duloxetine had no effect on male fertility, and effects in females were only evident at doses that caused maternal toxicity.

4.7. Effects on ability to drive and use machines.

The combination includes Pregabalin and Duloxetine, both of which may cause dizziness and somnolence, potentially impairing cognitive and motor functions.

Patients should avoid driving and operating hazardous machinery, especially when starting treatment or adjusting the dosage.

Methycobalamin alone does not typically cause impairment, but its combination with other components may still require caution.

Risk is heightened when combined with alcohol or other sedatives, increasing the chances of drowsiness and reduced alertness.

To ensure safety, patients should assess their tolerance to this combination before engaging in

activities requiring full mental and physical alertness.

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.

Table 1: Pregabalin adverse drug reactions

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

System Organ Class	Adverse drug reactions
	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
Not known	Respiratory depression
Gastrointestinal disorders	
Common	Vomiting, *nausea*, constipation, *diarrhoea,* flatule nce, abdominal distension, dry mouth
Uncommon	Gastroesophageal 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 papular, urticaria, hyperhidrosis, *pruritus*
Rare	Stevens *Johnson syndrome*, cold sweat
Common	Muscle cramp, arthralgia, back pain, pain in limb, cervical spasm

System Organ Class	Adverse drug reactions
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, 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).

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.

Duloxetine

The most commonly reported adverse reactions in patients treated with Cymbalta were nausea, headache, dry mouth, somnolence and dizziness. However, the majority of common adverse reactions were mild to moderate; they usually started early in therapy, and most tended to subside even as therapy was continued.

The below table gives the adverse reactions observed from spontaneous reporting and in placebo-controlled clinical trials.

Frequency estimate: 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).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table: Duloxetine Adverse drug reactions

Very common	Common	Uncommon	Rare	Very Rare
Infections and infestations				
		Laryngitis		
Immune system disorders				
			Anaphylactic reaction, Hypersensitivity disorder	
Endocrine disorders				
			Hypothyroidism	
Metabolism and nutrition disorders				
	Decreased appetite	Hyperglycaemia (reported especially in diabetic patients)	Dehydration, Hyponatraemia, SIADH	
Psychiatric disorders				
	Insomnia Agitation, Libido decreased, Anxiety, Orgasm abnormal, Abnormal dreams	Suicidal ideation, Sleep disorder, Bruxism, Disorientation, Apathy	Suicidal behaviour, Mania, Hallucinations, Aggression and anger	
Nervous system disorders				
Headache, Somnolence	Dizziness, Lethargy, Tremor, Paraesthesia	Myoclonus, Akathisia, Nervousness, Disturbance in attention, Dysgeusia, Dyskinesia, Restless legs syndrome, Poor quality sleep	Serotonin syndrome, Convulsion, Psychomotor restlessness, Extra-pyramidal symptoms,	
Eye disorders				

Very common	Common	Uncommon	Rare	Very Rare
	Blurred vision	Mydriasis, Visual impairment	Glaucoma	
Ear and labyrinth disorders				
	Tinnitus	Vertigo, Ear pain		
Cardiac disorders				
	Palpitations	Tachycardia, Supraventricular arrhythmia, mainly atrial fibrillation		
Vascular disorders				
	Blood pressure increase, Flushing	Syncope, Hypertension, Orthostatic hypotension, Peripheral coldness	Hypertensive crisis	
Respiratory, thoracic and mediastinal disorders				
	Yawning	Throat tightness, Epistaxis	Interstitial lung disease, Eosinophilic pneumonia	
Gastrointestinal disorders				
Nausea, Dry mouth	Constipation, Diarrhoea, Abdominal pain, Vomiting, Dyspepsia, Flatulence	Gastrointestinal haemorrhage, Gastroenteritis, Eructation, Gastritis, Dysphagia	Stomatitis, Haematochezia, Breath odour, Microscopic colitis	
Hepato-biliary disorders				
		Hepatitis, Elevated liver enzymes (ALT, AST, alkaline phosphatase), Acute liver injury	Hepatic failure, Jaundice	
Skin and subcutaneous tissue disorders				
	Sweating increased, Rash	Night sweats Urticaria,	Stevens-Johnson Syndrome,	

Very common	Common	Uncommon	Rare	Very Rare
		Dermatitis contact, Cold sweat, Photosensitivity reactions, Increased tendency to bruise	Angioneurotic oedema	
Musculoskeletal and connective tissue disorders				
	Musculoskeletal pain, Muscle spasm	Muscle tightness, Muscle twitching	Trismus	
Renal and urinary disorders				
	Dysuria, Pollakiuria	Urinary retention, Urinary hesitation, Nocturia, Polyuria, Urine flow decreased	Urine odour abnormal	
Reproductive system and breast disorders				
	Erectile dysfunction, Ejaculation disorder, Ejaculation delayed	Gynaecological haemorrhage, Menstrual disorder, Sexual dysfunction, Testicular pain	Menopausal symptoms Galactorrhoea, Hyper-prolactinaemia, Postpartum haemorrhage	
General disorders and administration site conditions				
	Falls, Fatigue,	Chest pain, Feeling abnormal, Feeling cold, Thirst, Chills, Malaise, Feeling hot, Gait disturbance		
Investigations				
	Weight decrease	Weight increase, Blood creatine phosphokinase increased.,	Blood cholesterol increased	

Very common	Common	Uncommon	Rare	Very Rare
		Blood potassium increased.		

Discontinuation of duloxetine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia or electric shock-like sensations, particularly in the head), sleep disturbances (including insomnia and intense dreams), fatigue, somnolence, agitation or anxiety, nausea and/or vomiting, tremor, headache, myalgia, irritability, diarrhoea, hyperhydrosis and vertigo are the most commonly reported reactions.

Methylcobalamin

Adverse events were reported in 13 of 2872 patients (0.45%). (At the end of the review period)

Clinically significant adverse events (unknown incidence)

Anaphylactoid reaction such as decreased blood pressure or dyspnea may occur. Patients should be carefully monitored. If such symptoms occur, treatment should be discontinued immediately, and appropriate measures taken.

Other adverse reactions:

	<0.1%	Incidence unknown
Hypersensitivity	Rash	
Other	Headache and warmth	Diaphoresis and pain/induration at intramuscular injection site

Note: If such symptoms occur, treatment should be discontinued.

A Multicentric, Randomized, Double Blind, Double Dummy, Prospective, Parallel Group, Comparative, Phase-III clinical trial of the FDC (Pregabalin, Methylcobalamin and Duloxetine (Delayed Release) Capsules) was conducted in 09 centers in India. In this study, a total of 215 subjects suffering from diabetic peripheral neuropathic pain coexisting with vitamin B12 deficiency were screened. A total of 26 adverse events (AEs) were reported.

Out of the 26 adverse events (AEs) reported, the distribution among the treatment arms was as follows:

- In Arm A (fixed-dose combination of Pregabalin 75 mg, Methylcobalamin 1500 mcg, and Duloxetine DR 20 mg capsules), there were 7 AEs. Of these, 2 were classified as probable/likely, and 5 were classified as unlikely.
- In Arm B (fixed-dose combination of Pregabalin 75 mg, Methylcobalamin 1500 mcg, and Duloxetine DR 30 mg capsules), 9 AEs were reported. Among these, 3 were classified as probable/likely, while 6 were classified as unlikely.
- In Arm C (fixed-dose combination of Pregabalin 75 mg, Methylcobalamin 1500 mcg, and Nortriptyline 10 mg tablets), 10 AEs were observed. Out of these, 4 were classified as probable/likely, and 6 were classified as unlikely.

Throughout the study, no serious adverse events (SAEs) or fatalities were reported. The adverse events included nausea, drowsiness, acidity, dry mouth, mouth ulcers, constipation, sedation, hypoglycemia, common cold, diarrhea, itching, and sneezing. Overall, there were no mortalities or SAEs reported in the treatment groups during the trial period.

Clinical Trial Study

A Multicentric, Randomized, Double Blind, Double Dummy, Prospective, Parallel Group, Comparative, Phase-III clinical trial was conducted at 09 centers in India. A total of 215 subjects suffering from diabetic peripheral neuropathic pain, coexisting with vitamin B12 deficiency, were screened. Four subjects withdrew their consent before randomization, and nine subjects failed the screening. Two hundred and two subjects were randomized using a computer-generated system into either of the study arms. . A total 66 subjects were randomized in the test arm A i.e. FDC of Pregabalin 75 mg + Methylcobalamin 1500 mcg + Duloxetine delayed release (DR) 20 mg capsules. In test arm A, 65 patients completed the study and 01 was lost to follow up. A total 68 patients were randomized in the test arm B i.e. FDC of Pregabalin 75 mg + Methylcobalamin 1500 mcg + Duloxetine DR 30 mg capsules, all 68 patients completed the study. In the reference arm C i.e. FDC of Pregabalin 75 mg + Methylcobalamin 1500 mcg + Nortriptyline 10 mg tablets, total 68 patients were randomized, out of which 67 completed the study and 01 was lost to follow up. The sites held prior approval from Institutional Ethics Committee for the conduct of the study.

The subjects were given study medication (tests or reference) at randomization visit/visit 2 and advised to take one capsule or one tablet once a daily orally every night at bedtime for 12 weeks of either FDC of Pregabalin 75 mg + Methylcobalamin 1500 mcg + Duloxetine DR 20 mg capsules or FDC of Pregabalin 75 mg + Methylcobalamin 1500 mcg + Duloxetine DR 30 mg capsules or FDC of Pregabalin 75 mg + Methylcobalamin 1500 mcg + Nortriptyline 10 mg tablets. The compliance was observed through patient diary. The subjects were also undergoing safety assessments. HbA1c and Routine Urine Analysis were performed at the screening visit/ visit 1. Laboratory tests including CBC, RFT (BUN, Serum Creatinine), eGFR, LFT (Total bilirubin, SGPT, SGOT), Serum electrolytes (Na+) were performed on screening Visit/ visit 1 and at the end of study visit/Visit 6 and Urine Pregnancy Test and ECG was performed at screening visit/ visit 1 and at the follow up visit/visit 5 to evaluate the safety. Vitals (Pulse, Temp., RR, BP), Physical Examination, ECG, performed at screening visit/ visit 1 and at the follow up visit/visit 5 to evaluate the safety. Visual Analog Scale (VAS), Leeds Assessment of Neuropathic Symptoms and Sign (LANSS) Pain Scale Score and Patient global impression of change (PGIC) Score were performed at all study visits and Vitamin B 12 assessment were performed at screening visit/ visit 1 and at the end of the study visit/ visit 6 to evaluate the efficacy.

The study met the primary efficacy parameter, the Mean change in visual analog scale (VAS) from baseline to end of the treatment (12 weeks) and the secondary efficacy parameter, change in Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) Pain Scale from baseline to end of treatment. (12 weeks), Change in the Patient global impression of change scores (PGIC) from baseline to end of the treatment. (12 Weeks), Change in Vitamin B12 level from baseline to end of the treatment (12 Weeks), and Consumption of rescue medication (number of Paracetamol Tablets consumed) during the study.

The results showed that visual analog scale (VAS) reduction was significantly greater at the end of study visit (12 weeks) for FDC of Pregabalin 75 mg + Methylcobalamin 1500 mcg + Duloxetine DR 30 mg capsules as compared to FDC of Pregabalin 75 mg + Methylcobalamin 1500 mcg + Duloxetine DR 20 mg capsules and FDC of Pregabalin 75 mg + Methylcobalamin 1500 mcg + Nortriptyline 10 mg tablets ($P < 0.00001$). While comparing the mean change in Leeds Assessment of Neuropathic Sign AND Symptoms Pain Scale (LANSS) from baseline to end of study visit (12 week), statistically significant difference was observed for FDC of Pregabalin 75 mg + Methylcobalamin 1500 mcg + Duloxetine DR 30 mg capsules as compared to FDC of Pregabalin 75 mg + Methylcobalamin 1500 mcg + Duloxetine DR 20 mg capsules and FDC of Pregabalin 75 mg + Methylcobalamin 1500 mcg +Nortriptyline 10 mg tablets. (P<

0.00001). At the end of the study visit (12-week) treatment period, the Patient Global Impression of Changes (PGIC) scores show variability among the treatment arms. For the "Very much improved" category, arm B had the highest proportion of patients (72.06%) reporting significant improvement, compared to 64.62% in arm A and 52.24% in arm C. This difference was statistically significant (P = 0.0552). In the "Much improved" category, arm C had the highest proportion (32.84%) compared to 26.15% in arm A and 22.06% in arm B, although the differences were not statistically significant (P = 0.3636). The "Minimally improved" category was highest in arm C (14.93%) versus 9.23% in arm A and 5.88% in arm B, with no significant difference (P = 0.2091).

The FDCs of Pregabalin 75 mg + Methylcobalamin 1500 mcg + Duloxetine DR 30 mg capsules and Pregabalin 75 mg + Methylcobalamin 1500 mcg + Duloxetine DR 20 mg capsules were observed to be statistically significantly superior to the FDC of Pregabalin 75 mg + Methylcobalamin 1500 mcg + Nortriptyline 10 mg tablets in the treatment of patients with diabetic peripheral neuropathic pain coexisting with Vitamin B12 deficiency."

FDC of Pregabalin 75 mg + Methylcobalamin 1500 mcg + Duloxetine DR 30 mg capsules was superior (statistically significant) to FDCs of Pregabalin 75 mg + Methylcobalamin 1500 mcg + Duloxetine 20 mg capsules and FDC of Pregabalin 75 mg + Methylcobalamin 1500 mcg + Nortriptyline 10 mg tablets, in the treatment of patients with diabetic peripheral neuropathic pain coexisting with a Vitamin B 12 deficiency.

The FDC of Pregabalin 75 mg + Methylcobalamin 1500 mcg + Duloxetine DR 20 mg capsules was superior (statistically significant) to FDC of Pregabalin 75 mg + Methylcobalamin 1500 mcg + Nortriptyline 10 mg tablets in the treatment of patients with diabetic peripheral neuropathic pain coexisting with a Vitamin B 12 deficiency. The FDCs of Pregabalin 75 mg + Methylcobalamin 1500 mcg + Duloxetine DR 30 mg capsules, Pregabalin 75 mg + Methylcobalamin 1500 mcg + Duloxetine DR 20 mg capsules and Pregabalin 75 mg + Methylcobalamin 1500 mcg + Nortriptyline 10 mg tablets were well tolerated and safe in all the treated subjects which having diabetic peripheral neuropathic pain coexisting with a Vitamin B 12 deficiency.

A total of 26 AEs were reported. In Arm A (fixed-dose combination of Pregabalin 75 mg, Methylcobalamin 1500 mcg, and Duloxetine DR 20 mg capsules), there were 7 AEs. Of these, 2 were classified as probable/likely, and 5 were classified as unlikely. In Arm B (fixed-dose combination of Pregabalin 75 mg, Methylcobalamin 1500 mcg, and Duloxetine DR 30 mg capsules), 9 AEs were reported. Among these, 3 were classified as probable/likely, while 6 were classified as unlikely. In Arm C (fixed-dose combination of Pregabalin 75 mg, Methylcobalamin 1500 mcg, and Nortriptyline 10 mg tablets), 10 AEs were observed. Out of these, 4 were classified as probable/likely, and 6 were classified as unlikely. Throughout the study, no serious adverse events (SAEs) or fatalities were reported. The adverse events included nausea, drowsiness, acidity, dry mouth, mouth ulcers, constipation, sedation, hypoglycemia, common cold, diarrhea, itching, and sneezing. Overall, there were no mortalities or SAEs reported in the treatment groups during the trial period.

Reporting of adverse reactions

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: https://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 postmarketing 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.

Duloxetine

Cases of overdoses, alone or in combination with other medicinal products, with duloxetine doses of 5400 mg were reported. Some fatalities have occurred, primarily with mixed overdoses, but also with duloxetine alone at a dose of approximately 1000 mg. Signs and symptoms of overdose (duloxetine alone or in combination with other medicinal products) included somnolence, coma, serotonin syndrome, seizures, vomiting and tachycardia.

No specific antidote is known for duloxetine, but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered. A free airway should be established. Monitoring of cardiac and vital signs is recommended, along with appropriate symptomatic and supportive measures. Gastric lavage may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal may be useful in limiting absorption. Duloxetine has a large volume of distribution and forced diuresis, haemoperfusion, and exchange perfusion are unlikely to be beneficial.

Methylcobalamin

Vitamin B12 is a water-soluble vitamin, and the risks of dose-related side effects are low. Your body can usually get rid of excess vitamin B12 through your urine. In rare cases, high doses of vitamin B12 injections have been associated with skin reactions. This isn't the case for oral vitamin B12 dietary supplements.

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.

Duloxetine

Duloxetine is a combined serotonin (5-HT) and noradrenaline (NA) reuptake inhibitor. It weakly inhibits dopamine reuptake, with no significant affinity for histaminergic, dopaminergic, cholinergic, and adrenergic receptors. Duloxetine dose-dependently increases extracellular levels of serotonin and noradrenaline in various brain areas of animals.

Methylcobalamin

Methylcobalamin is a neurotrope and acts as a growth promoter for nerve cells, a property that helps regenerate damaged central and peripheral nervous tissue in a disorder such as diabetic peripheral neuropathy. Methylcobalamin acts as a methyl donor for the synthesis of lecithin, a major component of the myelin sheath.

5.2. Pharmacodynamic properties

Pregabalin

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

Duloxetine

Clinical studies have shown that duloxetine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a less potent inhibitor of dopamine reuptake. Duloxetine has no significant affinity for dopaminergic, adrenergic, cholinergic, histaminergic, opioid, glutamate, and GABA receptors in vitro. Duloxetine does not inhibit monoamine oxidase (MAO). Duloxetine is in a class of drugs known to affect urethral resistance. If symptoms of urinary hesitation develop during treatment with Duloxetine, consideration should be given to the possibility that they might be drug related**.**

Methylcobalamin

- Methylcobalamin is a neurotrope and acts as a growth promoter for nerve cells, a property that helps regenerate damaged central and peripheral nervous tissue in a disorder such as diabetic peripheral neuropathy.
- Methylcobalamin acts as a methyl donor for the synthesis of lecithin, a major component of the myelin sheath.
- Methylcobalamin facilitates the methylation of tRNA which plays a fundamental role in protein synthesis and stimulates methionine synthesis and helps restore normal RNA levels in nerve cells.
- Methylcobalamin acts as a cofactor in the enzyme methionine synthase which regenerates methionine thus generating an increased supply of S-adenosyl methionine (SAMe) which protects against neurotoxicity.
- Methylcobalamin normalizes nerve cell conduction by healing damaged nerve cells and restores delayed synaptic transmission and decreased neurotransmitters to normal.
- Methylcobalamin improves the excitability of nerve fibers and thus improves neurotransmission.

5.3. Pharmacokinetic properties

ABSORPTION

Pregabalin

Following oral administration of FDC the mean plasma concentration Cmax was observed as 2385.466 ng/ml and median value of Tmax was observed as 0.750 hours**.**

Duloxetine

The mean plasma concentration Cmax was observed as 41.023 ng/ml and median value of Tmax was observed as 5.000 hours.

Methylcobalamin

The mean plasma concentration Cmax was observed as 917.204 ng/ml and median value of Tmax was observed as 2.000 hours**.**

Distribution and Metabolism

Pregabalin

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**.**

Duloxetine

Duloxetine is approximately 96% bound to human plasma proteins. Duloxetine binds to both albumin and alpha1-acid glycoprotein. Protein binding is not affected by renal or hepatic impairment.

Methylcobalamin

It is distributed to every cell of the body upon binding to Transcobalamine II, a B-globulin carrier protein and is stored in the liver in an amount of 300- 500 microgram. It is eliminated through bile.

Vitamin B12 is bound to specific plasma proteins called transcobalamins. Vitamin B12 is stored in the liver. It diffuses across the placenta and appears in breast milk also**.**

Elimination

Pregabalin

The half-life (t1/2) was measured at an average of 6.064 hours**.**

Duloxetine

The half-life (t1/2) was measured at an average of 15.441.

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.

Duloxetine

Carcinogenesis:

Duloxetine was administered in the diet to mice and rats for 2 years. In female mice receiving duloxetine at 140 mg/kg/day (11 times the maximum recommended human dose [MRHD, 60 mg/day] and 6 times the human dose of 120 mg/day on a mg/m2 basis), there was an increased incidence of hepatocellular adenomas and carcinomas. The no-effect dose was 50 mg/kg/day (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m2 basis). Tumor incidence was not increased in male mice receiving duloxetine at doses up to 100 mg/kg/day (8 times the MRHD and 4 times the human dose of 120 mg/day on a mg/m2 basis). In rats, dietary doses of duloxetine up to 27 mg/kg/day in females (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m2 basis) and up to 36 mg/kg/day in males (6 times the MRHD and 3 times the human dose of 120 mg/day on a mg/m2 basis) did not increase the incidence of tumors.

Mutagenesis:

Duloxetine was not mutagenic in the in vitro bacterial reverse mutation assay (Ames test) and was not clastogenic in an in vivo chromosomal aberration test in mouse bone marrow cells. Additionally, duloxetine was not genotoxic in an in vitro mammalian forward gene mutation assay in mouse lymphoma cells or in an in vitro unscheduled DNA synthesis (UDS) assay in primary rat hepatocytes and did not induce sister chromatid exchange in Chinese hamster bone marrow in vivo.

Impairment of Fertility

Duloxetine administered orally to either male or female rats prior to and throughout mating at doses up to 45 mg/kg/day (7 times the maximum recommended human dose of 60 mg/day and 4 times the human dose of 120 mg/day on a mg/m2 basis) did not alter mating or fertility.

Methylcobalamin

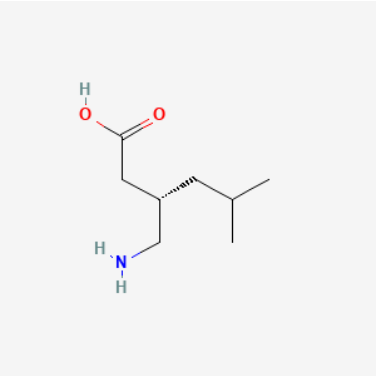
Animal data

In animal models of vitamin B12-related neuropathy, ultra-high dose methylcobalamin (500 mcg/kg) resulted in regeneration of motor neurons.

7. Description

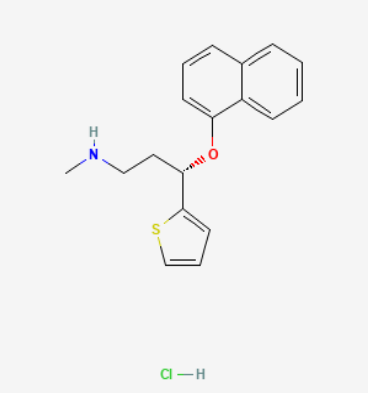
Pregabalin:

Pregabalin is (3S)-3-(aminomethyl)-5-methylhexanoic acid. The empiric formula of $C_8H_{17}NO_2$ and its molecular weight is 159.23 g/mol. Its structural formula is:



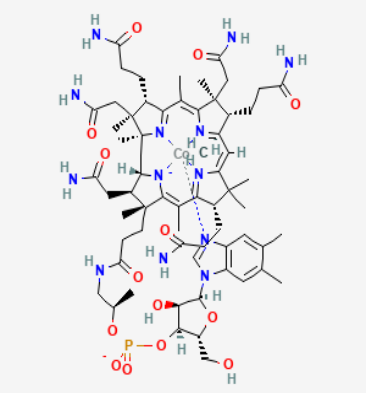
Duloxetine Hydrochloride:

Duloxetine Hydrochloride is 3S)-N-methyl-3-naphthalen-1-yloxy-3-thiophen-2-ylpropan-1-amine; hydrochloride The empiric formula of $C_{18}H_{20}ClNOS$ and its molecular weight is 333.9 g/mol. Its structural formula is:



Methylcobalamin:

Methylcobalamin is Coα-[α-(5,6-dimethyl-1H-benzoimidazole-1-yl)]-Coβ-methylcobamide. The empiric formula of $C_{63}H_{91}CoN_{13}O_{14}P^{-3}$ and its molecular weight is 1344.4g/mol. Its structural formula is:



PREGABA DM/ PREGALIN DM / PREGEB DM 75+20

Pregabalin, Methylcobalamin & Duloxetine (Delayed Release) Capsules is Red/Black coloured, size (1) capsule filled with light pink coloured granules of Pregabalin, Methylcobalamin and Off white spherical Enteric coated pellets of Duloxetine.

PREGABA DM/ PREGALIN DM / PREGEB DM 75+30

Pregabalin, Methylcobalamin & Duloxetine (Delayed Release) Capsules is Orange/Black coloured, size (1) capsule filled with light pink coloured granules of Pregabalin, Methylcobalamin and Off white spherical Enteric coated pellets of Duloxetine.

The excipients used are Lactose, Maize starch and Purified Talc.

8. Pharmaceutical particulars

8.1. Incompatibilities

Not applicable

8.2. Shelf-life

Do not use later than date of expiry.

8.3. Packaging information

PREGABA DM/ PREGALIN DM / PREGEB DM is packed in 10 Capsules.

8.4. Storage and handing instructions

Store at a temperature not exceeding 30^{o}C. Protect from light and moisture.

Keep all the medicine out of reach of children.

Capsule to be swallowed whole and not to be chewed or crushed.

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

Ravenbhel Healthcare Pvt. Ltd

16-17, EPIP, SIDCO, Kartholi- Bari Brahmana, Jammu

11. Details of permission or licence number with date

Mfg Lic No. JK/01/57 issued on: 19.06.2025.

12. Date of revision

OCT 2025

MARKETED BY