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

PREGEB FORTE 75

1. Generic Name:

Pregabalin, Methylcobalamin, Alpha Lipoic Acid, Pyridoxine Hydrochloride and Folic Acid Capsules

2. Qualitative and quantitative composition:

Each hard gelatin capsule contains:

Pregabalin I.P……....……...75 mg

Methylcobalamin I.P ….....750 mcg

Alpha Lipoic Acid I.P….....100 mg

Pyridoxine Hydrochloride I.P……...3 mg

Folic Acid I.P ……...….....1.5 mg

Excipients.....q.s.

Approved colours used in empty capsule shells

The excipients used are Dicalcium Phosphate, Microcrystalline Cellulose, Talcum, Magnesium Staearte, Colloidal Silicon Dioxide, Sodium Lauryl Sulphate, Croscarmellose Sodium.

3. Dosage form and strength:

Dosage form: Hard gelatin capsule

Strength: Pregabalin 75 mg, Methylcobalamin 750 mcg, Alpha Lipoic Acid 100 mg, Pyridoxine Hydrochloride 3 mg, Folic Acid 1.5 mg

4. Clinical particulars:

4.1 Therapeutic indication:

PREGEB FORTE is indicated for the treatment of painful diabetic neuropathy in adults only.

4.2 Posology and method of administration:

One tablet daily or as recommended by physician.

For pregabalin

The required dosage should be given in either two or three divided doses.

Pregabalin treatment can be started at a dose of 150 mg per day given as two or three divided doses. 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 600 mg per day after an additional 7-day interval.

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

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

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

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.

Pregabalin dose adjustment based on renal function.

Creatinine clearance (CLcr) (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

Patients with 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. No data are available.

Elderly (over 65 years of age) population
Elderly patients may require a dose reduction of pregabalin due to a decreased renal function.

Method of administration

Pregabalin may be taken with or without food.

4.3 Contraindications:

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

4.4 Special warnings and precautions for use:

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.

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.

Withdrawal of concomitant anti-epileptic medicinal products

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

Withdrawal symptoms

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

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

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

Congestive heart failure

There have been 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.

Suicidal ideation and behaviour

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

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

Reduced lower gastrointestinal tract function

There are postmarketing reports of events related to reduced lower gastrointestinal tract function (e.g. intestinal obstruction, paralytic ileus, constipation) when pregabalin was coadministered 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).

Misuse, abuse potential or dependence

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

Encephalopathy

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

Methylcobalamine

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

The treatment of vitamin B12 (parent compound of methylcobalamin) deficiency can unmask the symptoms of polycythemia vera.

Megaloblastic anemia is sometimes corrected by treatment with vitamin B12. But this can have very serious side effects. Don't attempt vitamin B12 therapy without close supervision by your healthcare provider.

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

Patients with vitamin B12 deficiency should not be treated with folic acid unless administered with adequate amounts of hydroxocobalamin, as it can mask the condition but the subacute irreversible damage to the nervous system will continue. The deficiency can be due to undiagnosed megaloblastic anaemia including in infancy, pernicious anaemia or macrocytic anaemia of unknown aethiology or other cause of cobalamin deficiency, including lifelong vegetarians.

Caution should be exercised when administering folic acid to patients who may have folate dependent tumours.

This product is not intended for healthy pregnant women where lower doses are recommended, but for pregnant women with folic acid deficiency or women at risk for the reoccurrence of neural tube defects.

Alpha lipoic acid

No data of relevance found.

Pyridoxin

This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum. Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 mcg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration. Single deficiency, as of pyridoxine alone, is rare. Multiple vitamin deficiency is to be expected in any inadequate diet. Patients treated with levodopa should avoid supplemental vitamins that contain more than 5 mg pyridoxine in the daily dose. Women taking oral contraceptives may exhibit increased pyridoxine requirements.

Folic acid

Administration of folic acid alone is improper therapy for pernicious anemia and other megaloblastic anemias in which vitamin B12 is deficient. Folic acid in doses above 0.1 mg daily may obscure pernicious anemia in that hematologic remission can occur while neurologic manifestations remain progressive. There is a potential danger in administering folic acid to patients with undiagnosed anemia, since folic acid may obscure the diagnosis of pernicious anemia by alleviating the hematologic manifestations of the disease while allowing the neurologic complications to progress. This may result in severe nervous system damage before the correct diagnosis is made. Adequate doses of vitamin B12 may prevent, halt, or improve the neurologic changes caused by pernicious anemia.

4.5 Drug-Interaction:

Pregabalin

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

In vivo studies and population pharmacokinetic analysis

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

Oral contraceptives, norethisterone and/or ethinyl oestradiol

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

Central nervous system influencing medical products

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

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

Interactions and the elderly

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

Pyridoxine hydrochloride

Pyridoxine supplements should not be given to patients receiving levodopa, because the action of the latter drug is antagonized by pyridoxine. However, this vitamin may be used concurrently in patients receiving a preparation containing both carbidopa and levodopa. Pyridoxine reduces the activity of altretamine. It has also been reported to decrease serum concentrations of phenobarbital and phenytoin.

Alpha lipoic acid

No data of relevance found.

Folic acid

There is evidence that the anticonvulsant action of phenytoin is antagonized by folic acid. A patient whose epilepsy is completely controlled by phenytoin may require increased doses to prevent convulsions if folic acid is given. Folate deficiency may result from increased loss of folate, as in renal dialysis and/or interference with metabolism (e.g. folic acid antagonists such as methotrexate); the administration of anticonvulsants, such as diphenylhydantoin, primidone, and barbiturates; alcohol consumption and, especially alcoholic cirrhosis; and the administration of pyrimethamine and nitrofurantoin. False low serum and red cell folate levels may occur if the patient has been taking antibiotics, such as tetracycline, which suppress the growth of Lactobacillus casei.

4.6 Use in special populations (Fertility, Pregnancy And Lactation)

Pragabalin

Women of childbearing potential/Contraception in males and females

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

Pregnancy

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

Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.

Pregabalin should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the foetus).

Breast-feeding

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

Fertility

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

In a 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 reported 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.

Limited data evidences available for Methylcobalamin, Alpha Lipoic Acid, Pyridoxine Hydrochloride and Folic Acid.

4.7 Effects on ability to drive and use machines:

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

4.8 Undesirable effects:

Pregabalin

The pregabalin clinical programme involved over 8,900 patients exposed to pregabalin, of whom over 5,600 were in double-blind placebo controlled trials. The most commonly reported adverse reactions were dizziness and somnolence. Adverse reactions were usually mild to moderate in intensity. In all controlled studies, the discontinuation rate due to adverse reactions was 12% for patients receiving pregabalin and 5% for patients receiving placebo. The most common adverse reactions resulting in discontinuation from pregabalin treatment groups were dizziness and somnolence.

In table 2 below all adverse reactions, which occurred at an incidence greater than placebo and in more than one patient, are listed by class and frequency (very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

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

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

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

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

Pregabalin and 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 attention, paraesthesia, hypoaesthesia, sedation, balance disorder, lethargy

Uncommon	Syncope, stupor, myoclonus, *loss of consciousness*, psychomotor hyperactivity, dyskinesia, dizziness postural, intention tremor, nystagmus, cognitive disorder, *mental impairment*, speech disorder, hyporeflexia, hyperaesthesia, burning sensation, ageusia, *malaise*
Rare	*Convulsions*, parosmia, hypokinesia, dysgraphia
Eye disorders	
Common	Vision blurred, diplopia
Uncommon	Peripheral vision loss, visual disturbance, eye swelling, visual field defect, visual acuity reduced, eye pain, asthenopia, photopsia, dry eye, lacrimation increased, eye irritation
Rare	*Vision loss, keratitis*, oscillopsia, altered visual depth perception, mydriasis, strabismus, visual brightness
Ear and labyrinth disorders	
Common	Vertigo
Uncommon	Hyperacusis
Cardiac disorders	
Uncommon	Tachycardia, atrioventricular block first degree, sinus bradycardia, *congestive heart failure*
Rare	QT prolongation, sinus tachycardia, sinus arrhythmia
Vascular disorders	

Uncommon	Hypotension, hypertension, hot flushes, flushing, peripheral coldness
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness
Rare	*Pulmonary oedema,* throat tightness
Gastrointestinal disorders	
Common	Vomiting, *nausea,* constipation, *diarrhoea,* flatulence, abdominal distension, dry mouth
Uncommon	Gastrooesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral
Rare	Ascites, pancreatitis, *swollen tongue,* dysphagia
Skin and subcutaneous tissue disorders	
Uncommon	Rash papular, urticaria, hyperhidrosis, *pruritus*
Rare	*Stevens Johnson syndrome,* cold sweat
Musculoskeletal and connective tissue disorders	
Common	Muscle cramp, arthralgia, back pain, pain in limb, cervical spasm
Uncommon	Joint swelling, myalgia, muscle twitching, neck pain, muscle stiffness
Rare	Rhabdomyolysis
Renal and urinary disorders	
Uncommon	Urinary incontinence, dysuria
Rare	Renal failure, oliguria, *urinary retention*
Reproductive system and breast disorders	
Common	Erectile dysfunction
Uncommon	Sexual dysfunction, ejaculation delayed, dysmenorrhoea, breast pain
Rare	Amenorrhoea, breast discharge, breast enlargement, *gynaecomastia*
General disorders and administration site conditions	

Common	Oedema peripheral, oedema, gait abnormal, fall, feeling drunk, feeling abnormal, fatigue
Uncommon	Generalised oedema, *face oedema*, chest tightness, pain, pyrexia, thirst, chills, asthenia
Investigations	
Common	Weight increased
Uncommon	Blood creatine phosphokinase increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood glucose increased, platelet count decreased, blood creatinine increased, blood potassium decreased, weight decreased
Rare	White blood cell count decreased

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

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

Paediatric population

The pregabalin safety profile observed in two reported paediatric studies (pharmacokinetic and tolerability study, n=65; 1-year open label follow on safety study, n=54) was similar to that observed in the adult studies.

Methylcobalamine

- Pulmonary edema and congestive heart failure early in treatment; peripheral vascular thrombosis.
- Polycythemia vera, mild transient diarrhea, rarely itching; transitory exanthema.
- Other adverse effects reported with vitamin B12 are diarrhea, blood clots, itching, serious allergic reactions.

Alpha Lipoic Acid

Alpha-lipoic acid is possibly safe for most adults when taken by mouth, when used intravenously or when applied to the skin. People taking alpha-lipoic acid by mouth might get a rash. People at risk for thiamine deficiency should take a thiamine supplement. People with diabetes should be careful to check their blood sugar levels because alpha-lipoic acid might lower blood sugar.

Folic Acid

High doses of folic acid might cause abdominal cramps, diarrhea, rash, sleep disorders, irritability, confusion, nausea, stomach upset, behavior changes, skin reactions, seizures, gas, excitability, and other side effects.

There is some concern that taking too much folic acid for a long period of time might cause serious side effects. Some research suggests that taking folic acid in doses of 800-1200 mcg might increase

the risk of heart attack in people who have heart problems. Other research suggests that taking these high doses might also increase the risk of cancer such as lung or prostate cancer.

Pyridoxine

In some people, pyridoxine might cause nausea, vomiting, stomach pain, loss of appetite, headache, tingling, sleepiness, and other side effects. Long-term use of high doses is possibly unsafe. It might cause certain brain and nerve problems.

Reporting of side effects:

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

http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

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.

Alpha lipoic acid

No data of relevance found.

Methylcobalamine

No data of relevance found.

Pyridoxine hydrochloride

Pyridoxine given to animals in amounts of 3 to 4 g/kg of body weight produces convulsions and death. In man, a dose of 25 mg/kg of body weight is well tolerated.

Folic acid

Except during pregnancy and lactation, folic acid should not be given in therapeutic doses greater than 0.4 mg daily until pernicious anemia has been ruled out. Patients with pernicious anemia receiving more than 0.4 mg of folic acid daily who are inadequately treated with vitamin B12 may show reversion of the hematologic parameters to normal, but neurologic manifestations due to vitamin B12 deficiency will progress. Doses of folic acid exceeding the Recommended Dietary Allowance (RDA) should not be included in multivitamin preparations; if therapeutic amounts are necessary, folic acid should be given separately.

5. Pharmacological properties:

5.1 Mechanism of Action:

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

5.2 Pharmacodynamic properties:

Pharmacotherapeutic group: Anti-epileptics, other anti-epileptics ATC code: N03AX16. The active substance, pregabalin, is a gamma-aminobutyric acid analogue [(S)-3(aminomethyl)-5-methylhexanoic acid].

Clinical efficacy and safety

Neuropathic pain

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

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

In 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.

Epilepsy

Adjunctive Treatment

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

Paediatric population

Reportedly, The efficacy and safety of pregabalin as adjunctive treatment for epilepsy in paediatric patients below the age of 12 and adolescents has not been established. The adverse events observed in a pharmacokinetic and tolerability study that enrolled patients from 3 months to 16 years of age (n=65) were similar to those observed in adults. Results of a 1-year open label safety study in 54 paediatric patients from 3 months to 16 years of age with epilepsy indicate that the adverse events of pyrexia and upper respiratory infections were observed more frequently than in adult studies.

Monotherapy (newly diagnosed patients)

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

Generalised Anxiety Disorder

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

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

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

In 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. Ophthamologic testing (including visual acuity testing, formal visual field testing and dilated funduscopic examination) was conducted in over 3600 patients within controlled clinical trials. In these patients, visual acuity was reduced in 6.5% of patients treated with pregabalin, and 4.8% of placebo-treated patients. Visual field changes were detected in 12.4% of pregabalin-treated, and 11.7% of placebo-treated patients. Funduscopic changes were observed in 1.7% of pregabalin-treated and 2.1% of placebo-treated patients.

Methylcobalamin

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

Alpha-lipoic acid

Alpha-lipoic acid is a vitamin-like chemical called an antioxidant. Yeast, liver, kidney, spinach, broccoli, and potatoes are good sources of alpha-lipoic acid. It is also made in the laboratory for use as medicine.

Alpha-lipoic acid is used for diabetes and nerve-related symptoms of diabetes including burning, pain, and numbness in the legs and arms.

Alpha-lipoic acid seems to help prevent certain kinds of cell damage in the body, and also restores vitamin levels such as vitamin E and vitamin C. There is also evidence that alphalipoic acid can improve the function and conduction of neurons in diabetes.

Alpha-lipoic acid is used in the body to break down carbohydrates and to make energy for the other organs in the body.

Alpha-lipoic acid seems to work as an antioxidant, which means that it might provide protection to the brain under conditions of damage or injury. The antioxidant effects might also be helpful in certain liver diseases.

Pyridoxine Hydrochloride

Pyridoxine hydrochloride is Vitamin B6. It is converted to pyridoxal phosphate which is the co-enzyme for a variety of metabolic transformations. It is essential for human nutrition.

Methylcobalamin

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

Folic Acid

Folic acid is a member of the vitamin B group. Folic acid is reduced in the body to tetrahydrofolate, which is a coenzyme for various metabolic processes including the synthesis of purine and pyrimidine nucleotides, and hence in the synthesis of DNA; it is also involved in some amino-acid conversions.

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 readily absorbed when administered in the fasted state, with peak plasma concentrations occurring within 1 hour following both single and multiple dose administration. Pregabalin oral bioavailability is estimated to be ≥ 90% and is independent of dose. Following repeated administration, steady state is achieved within 24 to 48 hours. The rate of pregabalin absorption is decreased when given with food resulting in a decrease in C_{max} by approximately 25-30% and a delay in t_{max} to approximately 2.5 hours. However, administration of pregabalin with food has no clinically significant effect on the extent of pregabalin absorption.

Distribution

In preclinical studies, pregabalin has been shown to cross the blood brain barrier in mice, rats, and monkeys. Pregabalin has been shown to cross the placenta in rats and is present in the milk of lactating rats. In humans, the apparent volume of distribution of pregabalin following oral administration is approximately 0.56 l/kg. Pregabalin is not bound to plasma proteins.

Biotransformation

Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabelled pregabalin, approximately 98% of the radioactivity recovered in the urine was unchanged pregabalin. The N-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0.9% of the dose. In preclinical studies, there was no indication of 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 reported pharmacokinetic and tolerability study.

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

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

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

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

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

Elderly

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

Breast-feeding mothers

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

Alpha Lipoic Acid

It is reported that alpha-lipoic acid 600 mg was administered orally once daily for 4 days, and the pharmacokinetic parameters were measured on days 1 and 4 revealed the mean percentage of the

administered dose excreted in urine as parent compound was 0.2 (which is 0.67% with assumption of 30% bioavailability).

Pyridoxine Hydrochloride

Pyridoxine readily absorbed from the gastrointestinal tract after oral dose and converted to the active forms pyridoxal phosphate and pyridoxamine phosphate. They are stored mainly in the liver where there is oxidation to 4-pyridoxic acid and other inactive metabolites which are excreted in the urine. As the dose increases, proportionally greater amounts are excreted unchanged in the urine. Pyridoxal crosses the placenta and is distributed into breast milk.

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 transcobalamins; transcobalamin 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 also appears in breast milk.

Folic acid

Folic acid is rapidly absorbed from the gastrointestinal tract, mainly from the duodenum and jejunum. Dietary folates are stated to have about half the bioavailability of crystalline folic acid. The naturally occurring folate polyglutamates are largely deconjugated, and then reduced by dihydrofolate reductase in the intestines to form 5-methyltetrahydrofolate, which appears in the portal circulation, where it is extensively bound to plasma proteins. Folic acid given therapeutically enters the portal circulation largely unchanged, since it is a poor substrate for reduction by dihydrofolate reductase. It is converted to the metabolically active form 5- methyltetrahydrofolate in the plasma and liver. The principal storage site of folate is the liver; it is also actively concentrated in the CSF. Folate undergoes enterohepatic circulation. Folate metabolites are eliminated in the urine and folate in excess of body requirements is excreted unchanged in the urine. Folate is distributed into breast milk. Folic acid is removed by haemodialysis.

6. Nonclinical properties:

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.

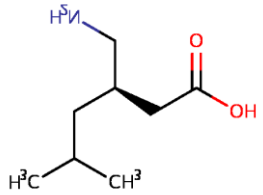
Two-year carcinogenicity studies with pregabalin were conducted in rats and mice. No tumours were observed in rats at exposures up to 24 times the mean human exposure at the maximum recommended clinical dose of 600 mg/day. In mice, no increased incidence of tumours was found at exposures similar to the 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.

No preclinical data of relevance found for Methylcobalamin, Alpha Lipoic Acid, Pyridoxine Hydrochloride and Folic Acid.

7. Description:

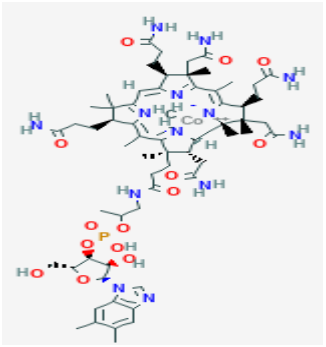
Pregabalin is a 3-isobutyl derivative of gamma-amino butyric acid (GABA) with anti-convulsant, anti-epileptic, anxiolytic, and analgesic activities. Pregabalin selectively binds to alpha2delta (A2D) subunits of presynaptic voltage dependent calcium channels (VDCCs) located in the central nervous system (CNS). It's molecular formula is $C_8H_{17}NO_2$ and molecular weight is 159.23 g/mol.



It is White to off-white crystalline solid, Freely soluble in water and both basic and acidic solutions.

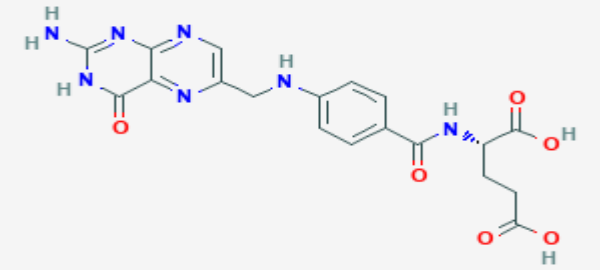
Methylcobalamin

Methylcobalamin is chemically, Coα- [α-(5,6-dimethyl-1H-benzoimidazole-1-yl)]-Coβ-methylcobamide with molecular weight of 1344.4 g/mol and empirical formula is $C_{63}H_{91}CoN_{13}O_{14}P$. The chemical structure is:



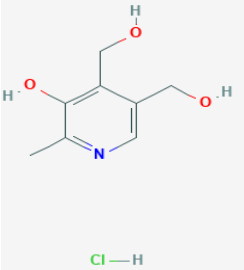
Folic Acid

Folic Acid is chemically, (2S)-2-[[4-[(2-amino-4-oxo-3H-pteridin-6-yl) methylamino]benzoyl]amino]pentanedioic acid with molecular weight of 441.4 g/mol and empirical formula is $C_{19}H_{19}N_7O_6$. The chemical structure is:



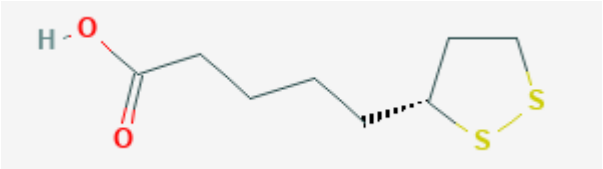
Pyridoxine Hydrocloride

Pyridoxine Hydrochloride is 4,5-bis(hydroxymethyl)-2-methylpyridin-3-ol;hydrochloride with molecular weight of 205.64 g/mol and empirical formula is $C_8H_{12}ClNO_3$. The chemical structure is:



Alpha Lipoic Acid

Alpha Lipoic Acid is 5-[(3R)-dithiolan-3-yl]pentanoic acid with molecular weight of 206.3 g/mol and empirical formula is $C_8H_{14}O_2S_2$. The chemical structure is:



Pregeb Forte capsules are Chocolate colour cap and body containing a size “1” hard gelatin capsule containing yellowish pinkish coloured granular powder with dark brown or black particles. The excipients used are Dicalcium Phosphate, Microcrystalline Cellulose, Talcum, Magnesium Staearte, Colloidal Silicon Dioxide, Sodium Lauryl Sulphate, Croscarmellose Sodium.

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:

PREGEB FORTE is available as blister pack of 10 Capsules in printed carton.

8.4 Storage and handing instructions:

Store below 25°C. Protect from light and moisture.

9. Patient Counselling Information

Package leaflet: Information for the user

PREGEB FORTE

Pregabalin, Methylcobalamin, Alpha Lipoic Acid, Pyridoxine Hydrochloride and Folic Acid Capsules

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

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 9.4.

What is in this leaflet?

9.1 What PREGEB FORTE is and what it is used for

PREGEB FORTE belongs to a group of medicines used to treat epilepsy, neuropathic pain and Generalised Anxiety Disorder (GAD) in adults.

PREGEB FORTE is indicated for the treatment of painful diabetic neuropathy in adults only.

9.2 What you need to know before you take PREGEB FORTE

Do not take PREGEB FORTE
If you are allergic to pregabalin or any of the other ingredients of this medicine.

Warnings and Precautions
Talk to your doctor or pharmacist before taking PREGEB FORTE
• Some patients taking PREGEB FORTE have reported symptoms suggesting an allergic reaction. These symptoms include swelling of the face, lips, tongue, and throat, as well as diffuse skin rash. Should you experience any of these reactions, you should contact your physician immediately.
• PREGEB FORTE has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in elderly patients. Therefore, you should be careful until you are used to any effect the medicine might have.
• PREGEB FORTE may cause blurring or loss of vision, or other changes in eyesight, many of which are temporary. You should immediately tell your doctor if you experience any changes in your vision.
• Some patients with diabetes who gain weight while taking pregabalin may need an alteration in their diabetic medicines.
• Certain side effects may be more common, such as sleepiness, because patients with spinal cordinjury may be taking other medicines to treat, for example, pain or spasticity, that have similar side effects to Pregabalin and the severity of these effects may be increased when taken together.
• There have been reports of heart failure in some patients when taking PREGEB FORTE; these patients were mostly elderly with cardiovascular conditions. Before taking this medicine you should tell your doctor if you have a history of heart disease.
• There have been reports of kidney failure in some patients when taking PREGEB FORTE. If while taking PREGEB FORTE you notice decreased urination, you should tell your doctor as stopping the medicine may improve this.
• A small number of people being treated with anti-epileptics such as PREGEB FORTE have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.
• When PREGEB FORTE is taken with other medicines that may cause constipation (such as some types of pain medicines) it is possible that gastrointestinal problems may occur (e.g., constipation, blocked or paralysed bowel). Tell your doctor if you experience constipation, especially if you are prone to this problem.
• Before taking this medicine you should tell your doctor if you have a history of alcoholism or any drug abuse or dependence. Do not take more medicine than prescribed.
• There have been reports of convulsions when taking PREGEB FORTE or shortly after stopping PREGEB FORTE. If you experience a convulsion, contact your doctor immediately.
• There have been reports of reduction in brain function (encephalopathy) in some patients taking PREGEB FORTE when they have other conditions. Tell your doctor if you have a history of any serious medical conditions, including liver or kidney disease.
• There have been reports of breathing difficulties. If you have nervous system disorders, respiratory disorders, renal impairment, or you are older than 65, your doctor may prescribe you a different dosing regimen. Contact your doctor if you experience trouble breathing or shallow breaths.

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

Other medicines and PREGEB FORTE
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.
PREGEB FORTE and certain other medicines may influence each other (interaction). When taken with certain other medicines which have sedative effects (including opioids), PREGEB FORTE may potentiate these effects and could lead to respiratory failure, coma and death. The degree of dizziness,

sleepiness and decreased concentration may be increased if PREGEB FORTE is taken together with medicines containing:
Oxycodone – (used as a pain-killer)
Lorazepam – (used for treating anxiety)
Alcohol
PREGEB FORTE may be taken with oral contraceptives
PREGEB FORTE with food, drink and alcohol PREGEB FORTE capsules may be taken with or without food.
It is advised not to drink alcohol while taking PREGEB FORTE
Pregnancy, breast-feeding and fertility
PREGEB FORTE should not be taken during pregnancy or when breast-feeding, unless you are told other wise by your doctor. Effective contraception must be used by women of child-bearing potential. If you are pregnant or breast-feeding,think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
Driving and using machines
PREGEB FORTE may produce dizziness, sleepiness and decreased concentration. You should not drive, operate complex machinery or engage in other potentially hazardous activities until you know whether this medicine affects your ability to perform these activities.
PREGEB FORTE contains Sodium:
This medicine contains less than 1 mmol sodium (23 mg) per each capsule, that is to say essentially 'sodium-free'.

9.3 How to take PREGEB FORTE

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Your doctor will determine what dose is appropriate for you.

PREGEB FORTE is for oral use only.

Peripheral and central neuropathic pain, epilepsy or Generalised Anxiety Disorder:

- Take the number of capsules as instructed by your doctor.
- The dose, which has been adjusted for you and your condition, will generally be between 150 mg and 600 mg each day.
- Your doctor will tell you to take PREGEB FORTE either twice or three times a day. For twice a day take PREGEB FORTE once in the morning and once in the evening, at about the same time each day. For three times a day take PREGEB FORTE once in the morning, once in the afternoon and once in the evening, at about the same time each day.
- If you have the impression that the effect of PREGEB FORTE is too strong or too weak, talk to your doctor or pharmacist.
- If you are an elderly patient (over 65 years of age), you should take PREGEB FORTE normally except if you have problems with your kidneys.
- Your doctor may prescribe a different dosing schedule and/or dose if you have problems with your kidneys.
- Swallow the capsule whole with water.
- Continue taking PREGEB FORTE until your doctor tells you to stop.

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

If you forget to take PREGEB FORTE

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

If you stop taking PREGEB FORTE

Do not stop taking PREGEB FORTE unless your doctor tells you to. If your treatment is stopped it should be done gradually over a minimum of 1 week.

After stopping long and short-term PREGEB FORTE treatment, you need to know that you may experience certain side effects. These include, trouble sleeping, headache, nausea, feeling anxious, diarrhoea, flu-like symptoms, convulsions, nervousness, depression, pain, sweating, and dizziness. These symptoms may occur more commonly or severely if you have been taking PREGEB FORTE for a longer period of time.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
Very common (may affect more than 1 in 10 people):
Dizziness, drowsiness, headache
Common (may affect up to 1 in 10 people):

- Increased appetite
- Feeling of elation, confusion, disorientation, decrease in sexual interest, irritability
- Disturbance in attention, clumsiness, memory impairment, loss of memory, tremor, difficulty with speaking,tingling feeling, numbness, sedation, lethargy, insomnia, fatigue, feeling abnormal
- Blurred vision, double vision
- Vertigo, problems with balance, fall
- Dry mouth, constipation, vomiting, flatulence, diarrhoea, nausea, swollen abdomen
- Difficulties with erection
- Swelling of the body including extremities
- Feeling drunk, abnormal style of walking
- Weight gain
- Muscle cramp, joint pain, back pain, pain in limb
- Sore throat
- Uncommon (may affect up to 1 in 100 people):
- Loss of appetite, weight loss, low blood sugar, high blood sugar.
- Change in perception of self, restlessness, depression, agitation, mood swings, difficulty finding words, hallucinations, abnormal dreams, panic attacks, apathy, aggression, elevated mood, mental impairment, difficulty with thinking, increase in sexual interest, problems with sexual functioning including inability to achieve a sexual climax, delayed ejaculation.

- Changes in eyesight, unusual eye movement, changes in vision including tunnel vision, flashes of light, jerky movements, reduced reflexes, increased activity, dizziness on standing, sensitive skin, loss of taste, burning sensation, tremor on movement, decreased consciousness, loss of consciousness, fainting, increased sensitivity to noise, feeling unwell.
- Dry eyes, eye swelling, eye pain, weak eyes, watery eyes, eye irritation.
- Heart rhythm disturbances, increased heart rate, low blood pressure, high blood pressure, changes in heart beat, heart failure.
- Flushing, hot flushes.
- Difficulty breathing, dry nose, nasal congestion.

- Increased saliva production, heartburn, numb around mouth.
- Sweating, rash, chills, fever.
- Muscle twitching, joint swelling, muscle stiffness, pain including muscle pain,neck pain.
- Breast pain.
- Difficulty with or painful urination, incontinence.
- Weakness, thirst, chest tightness.
- Changes in blood and liver test results (blood creatinine phosphokinase increased, alanine amino transferase increased, aspartate amino transferase increased, platelet count decreased, neutropaenia, increase in blood creatinine, decrease in blood potassium).
- Hypersensitivity, swollen face, itchiness, hives, runny nose, nose bleed, cough, snoring.
- Painful menstrual periods.
- Coldness of hands and feet.

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

- Abnormal sense of smell, swinging vision, altered perception of depth, visual brightness, vision loss.
- Dilated pupils, cross eyes.
- Cold sweat, tightness of the throat, swollen tongue.
- Inflammation of the pancreas.
- Difficulty in swallowing.
- Slow or reduced movement of the body.
- Difficulty with writing properly.
- Increased fluid in the abdomen.
- Fluid in the lungs
- Convulsions
- Changes in the recording of electrical changes (ECG) in the heart which correspond to heart rhythm disturbances
- Muscle damage.
- Breast discharge, abnormal breast growth, breast growth in males.
- Interrupted menstrual periods.
- Kidney failure, reduced urine volume, urinary retention.
- Decrease in white blood cell count.
- Inappropriate behaviour.
- Allergic reactions (which may include difficulty breathing, inflammation of the eyes (keratitis) and a serious skin reaction characterized by rash, blisters, peeling skin and pain).
- Jaundice (yellowing of the skin and eyes).

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

- Liver failure.
- Hepatitis (inflammation of the liver).

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

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

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

The following adverse reaction has been reported in the postmarketing experience: Trouble breathing, shallow breaths.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

9.5 How to store PREGEB FORTE

Store below 25°C. Protect from light and moisture.

9.6 Contents of the pack and other information

PREGEB FORTE is available as blister pack of 10 Capsules in printed carton.

What PREGEB FORTE contains

PREGEB FORTE contains Pregabalin, Methylcobalamin, Alpha Lipoic Acid, Pyridoxine Hydrochloride, Folic Acid.

Approved colour used in empty capsule shells

The excipients used are Dicalcium Phosphate, Microcrystalline Cellulose, Talcum, Magnesium Staearte, Colloidal Silicon Dioxide, Sodium Lauryl Sulphate, Croscarmellose Sodium.

10. Details of manufacturer

Manufactured by:

Innova Captab Ltd.

1281/1,

Hilltop Industrial Estate Near EPIP,

Phase-1, Jharmajri, Baddi, Dist. Solan (H.P)

11. Details of permission or licence number with date

Mfg Lic. No. MB/09/803 issued on 27.08.2020

12. Date of revision

MAY 2021

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/PREGEB FORTE 75 mg/MAY-21/05/PI