"To be sold by retail on the prescription of a R.M.P. only"

PREGEB D/ PREGABA-D/ PREGALIN D

1. Generic Name:

Pregabalin and Duloxetine Capsules

2. Qualitative and quantitative composition:

PREGEB D 50/20/ PREGABA-D 50/20/ PREGALIN D 50/20

Each hard gelatin capsule contains:

Pregabalin IP…….50 mg

Duloxetine Hydrochloride IP equivalent to Duloxetine…20 mg

(As delayed release pellets)

Excipients……. q.s.

Color: Titanium dioxide

Approved color used in hard gelatin capsule shells.

The other ingredients are: Starch, Talc, Sugar Spheres, Hypromellose, Sucrose, Hypromellose Acetate Succinate, Triethyl citrate, Polyethylene glycol 400 and Titanium dioxide SIZE "2" hard gelatin capsule.

PREGEB D 75/20/ PREGABA-D 75/20/ PREGALIN D 75/20

Each hard gelatin capsule contains:

Pregabalin IP…….75 mg

Duloxetine Hydrochloride IP equivalent to Duloxetine…20 mg

(As delayed release pellets)

Excipients……. q.s.

Color: Titanium dioxide

Approved color used in hard gelatin capsule shells.

The other ingredients are: Starch, Talc, Sugar Spheres, Hypromellose, Sucrose, Hypromellose Acetate Succinate, Triethyl citrate, Polyethylene glycol 400 and Titanium dioxide SIZE "1" hard gelatin capsule.

PREGEB D 75/30/ PREGABA-D 75/30/ PREGALIN D 75/30

Each hard gelatin capsule contains:

Pregabalin IP…….75 mg

Duloxetine Hydrochloride IP equivalent to Duloxetine…30 mg

(As delayed release pellets)

Excipients……. q.s.

Color: Titanium dioxide

Approved color used in hard gelatin capsule shells.

The other ingredients are: Starch, Talc, Sugar Spheres, Hypromellose, Sucrose, Hypromellose Acetate Succinate, Triethyl citrate, Polyethylene glycol 400 and Titanium dioxide SIZE "1" hard gelatin capsule.

3. Dosage form and strength

Dosage form: Hard gelatin capsules

Strength:

50mg+20mg: Pregabalin 50 mg, Duloxetine 20 mg

75mg+20mg: Pregabalin 75 mg, Duloxetine 20 mg

75mg+30mg: Pregabalin 75 mg, Duloxetine 30 mg

4. Clinical particulars

4.1 Therapeutic Indication

For the treatment of neuropathic pain.

4.2 Posology and Method of Administration

Pregabalin

Posology

Dose: The recommended dose range is pregabalin 50 mg + duloxetine 20 mg to pregabalin 150 mg + duloxetine 60 mg per day given as single dose or in two divided doses.
Treatment can be started at a dose of pregabalin 50 mg + duloxetine 20 mg per day. Based on individual patient response and tolerability, the dose may be increased to pregabalin 50 mg + duloxetine 20 mg twice a day, pregabalin 75 mg + duloxetine 20 mg per day, pregabalin 75 mg + duloxetine 20 mg twice a day, pregabalin 75 mg + duloxetine 30 mg per day after an interval of 3 to 7 days at each dose increment, and if needed, to a maximum dose of pregabalin 150 mg + duloxetine 60 mg per day after an additional 7-day interval.

Method of administration

Pregabalin and duloxetine may be taken with or without food.

Pregabalin and duloxetine is for oral use only.

4.3 Contraindications

- Known hypersensitivity to pregabalin, duloxetine or any of its components. Angioedema and hypersensitivity reactions have occurred in patients receiving pregabalin therapy.
- Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated due to the risk of serious, sometimes fatal, drug interactions with serotonergic drugs. These interactions may include hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued serotonin reuptake inhibitors and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome.

- Uncontrolled Narrow-Angle Glaucoma

4.4 Special warnings and precautions for use

Pregabalin

Angioedema
There have been post-marketing reports of angioedema in patients during initial and chronic treatment with pregabalin. Specific symptoms included swelling of the face, mouth (tongue, lips, and gums), and neck (throat and larynx). There were reports of life-threatening angioedema with respiratory compromise requiring emergency treatment. Discontinue this treatment immediately in patients with these symptoms. Exercise caution when prescribing pregabalin to patients who have had a previous episode of angioedema. In addition, patients who are taking other drugs associated with angioedema (e.g., angiotensin converting enzyme inhibitors) may be at increased risk of developing angioedema.

Hypersensitivity
There have been post-marketing reports of hypersensitivity in patients shortly after initiation of treatment with pregabalin. Adverse reactions included skin redness, blisters, hives, rash, dyspnea, and wheezing. Discontinue this treatment immediately in patients with these symptoms.

Increased Risk of Adverse Reactions with Abrupt or Rapid Discontinuation
Following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache, anxiety, hyperhidrosis, and diarrhea.

Suicidal Behavior and Ideation
Pregabalin increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Monitor patients for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Peripheral Edema
Pregabalin treatment may cause peripheral edema. In reported short-term trials of patients without clinically significant heart or peripheral vascular disease, there was no apparent association between peripheral edema and cardiovascular complications such as hypertension or congestive heart failure. Peripheral edema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function. Concomitant use with thiazolidinedione class of antidiabetic drugs can cause weight gain and/or fluid retention, possibly exacerbating or leading to heart failure, exercise caution when co-administering pregabalin and these agents. Because there are limited data on congestive heart failure patients with New York Heart Association Class III or IV cardiac status, exercise caution when using pregabalin in these patients.

Dizziness and Somnolence
Pregabalin may cause dizziness and somnolence. Inform patients that pregabalin related dizziness and somnolence may impair their ability to perform tasks such as driving or operating

machinery. Dizziness and somnolence generally began shortly after the initiation of pregabalin therapy and occurred more frequently at higher doses.

Weight Gain

Pregabalin treatment may cause weight gain. In reported pregabalin controlled clinical trials in adult patients of up to 14 weeks, a gain of 7% or more over baseline weight was observed in 9% of pregabalin-treated patients and 2% of placebo-treated patients.

Tumorigenic Potential

In standard preclinical *in vivo* lifetime carcinogenicity studies of pregabalin, an unexpectedly high incidence of hemangiosarcoma was identified in two different strains of mice. The clinical significance of this finding is unknown. In reported clinical studies across various patient populations, comprising 6396 patient-years of exposure in patients greater than 12 years of age, new or worsening-preexisting tumors were reported in 57 patients. Without knowledge of the background incidence and recurrence in similar populations not treated with pregabalin, it is impossible to know whether the incidence seen in these cohorts is or is not affected by treatment.

Ophthalmological Effects

In controlled studies in adult patients, a higher proportion of patients treated with pregabalin reported blurred vision (7%) than did patients treated with placebo (2%), which resolved in a majority of cases with continued dosing. Although the clinical significance of the ophthalmologic findings is unknown, inform patients to notify their physician if changes in vision occur. If visual disturbance persists, consider further assessment. Consider more frequent assessment for patients who are already routinely monitored for ocular conditions.

Creatine Kinase Elevations

Pregabalin treatment was associated with creatine kinase elevations. Mean changes in creatine kinase from baseline to the maximum value were 60 U/L for pregabalin treated patients and 28 U/L for the placebo patients. In all reported controlled trials in adult patients across multiple patient populations, 1.5% of patients on pregabalin and 0.7% of placebo patients had a value of creatine kinase at least three times the upper limit of normal. Three pregabalin treated subjects had events reported as rhabdomyolysis in reported premarketing clinical trials. The relationship between these myopathy events and pregabalin is not completely understood because the cases had documented factors that may have caused or contributed to these events. Instruct patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if these muscle symptoms are accompanied by malaise or fever. Discontinue treatment if myopathy is diagnosed or suspected or if markedly elevated creatine kinase levels occur.

Decreased Platelet Count

Pregabalin treatment was associated with a decrease in platelet count. Pregabalin treated subjects experienced a mean maximal decrease in platelet count of $20 \times 10^3/\mu L$, compared to $11 \times 10^3/\mu L$ in placebo patients. In the overall database of controlled trials in adult patients, 2% of placebo patients and 3% of pregabalin patients experienced a potentially clinically significant decrease in platelets, defined as 20% below baseline value and less than $150 \times 10^3/\mu L$. A single pregabalin treated subject developed severe thrombocytopenia with a platelet count less than $20 \times 10^3/ \mu L$.

PR Interval Prolongation
Pregabalin treatment was associated with PR interval prolongation. In analyses of reported clinical trial ECG data in adult patients, the mean PR interval increase was 3–6 msec at pregabalin doses greater than or equal to 300 mg/day. This mean change difference was not associated with an increased risk of PR increase greater than or equal to 25% from baseline, an increased percentage of subjects with on-treatment PR greater than 200 msec, or an increased risk of adverse reactions of second or third degree AV block

Duloxetine

Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults
Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that discontinuation can be associated with certain symptoms.

Families and caregivers of patients should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers.

Hepatotoxicity
There have been reports of hepatic failure, sometimes fatal, in patients treated with duloxetine. These cases have presented as hepatitis with abdominal pain, hepatomegaly, and elevation of transaminase levels to more than twenty times the upper limit of normal with or without jaundice, reflecting a mixed or hepatocellular pattern of liver injury. Duloxetine should be discontinued in patients who develop jaundice or other evidence of clinically significant liver dysfunction and should not be resumed unless another cause can be established.

Duloxetine increased the risk of elevation of serum transaminase levels in reported development program clinical trials. Liver transaminase elevations resulted in the discontinuation of 0.3% of duloxetine-treated patients.

Because it is possible that duloxetine and alcohol may interact to cause liver injury or that duloxetine may aggravate pre-existing liver disease, duloxetine should not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

Orthostatic Hypotension, Falls and Syncope
Orthostatic hypotension, falls and syncope have been reported with therapeutic doses of duloxetine. Syncope and orthostatic hypotension tend to occur within first week of therapy but can occur at any time during duloxetine treatment, particularly after dose increases. The risk of falling appears to be related to the degree of orthostatic decrease in blood pressure as well as other factors that may increase the underlying risk of falls. The risk of blood pressure decreases

may be greater in patients taking concomitant medications that induce orthostatic hypotension (such as antihypertensives) or are potent CYP1A2 inhibitors. Consideration should be given to dose reduction or discontinuation of duloxetine in patients who experience symptomatic orthostatic hypotension, falls and/or syncope during duloxetine therapy. Risk of falling also appeared to be proportional to a patient's underlying risk for falls and appeared to increase steadily with age. As elderly patients tend to have a higher underlying risk for falls due to a higher prevalence of risk factors such as use of multiple medications, medical comorbidities and gait disturbances, the impact of increasing age by itself is unclear.

Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome has been reported with SNRIs and SSRIs, including duloxetine, alone but particularly with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines, and St. John's Wort) and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

Serotonin syndrome symptoms may include mental status changes (e.g., agitation hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, and hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome. Treatment with duloxetine and any concomitant serotonergic agents, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

Abnormal Bleeding

SSRIs and SNRIs, including duloxetine, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anti-coagulants may add to this risk. Case reports and epidemiological studies have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages. Patients should be cautioned about the risk of bleeding associated with the concomitant use of duloxetine and NSAIDs, aspirin, or other drugs that affect coagulation.

Severe Skin Reactions

Severe skin reactions, including erythema multiforme and Stevens-Johnson Syndrome (SJS), can occur with duloxetine. The reporting rate of SJS associated with duloxetine use exceeds the general population background incidence rate for this serious skin reaction (1 to 2 cases per million person years). Duloxetine should be discontinued at the first appearance of blisters, peeling rash, mucosal erosions, or any other sign of hypersensitivity if no other etiology can be identified.

Discontinuation of Treatment with Duloxetine

Discontinuation symptoms have been systematically evaluated in patients taking duloxetine. Following abrupt or tapered discontinuation in reported adult placebo-controlled clinical trials, the following symptoms occurred at 1% or greater and at a significantly higher rate in duloxetine-treated patients compared to those discontinuing from placebo: dizziness, headache, nausea, diarrhea, paresthesia, irritability, vomiting, insomnia, anxiety, hyperhidrosis, and

fatigue. Patients should be monitored for these symptoms when discontinuing treatment with duloxetine. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

Activation of Mania/Hypomania
Duloxetine should be used cautiously in patients with a history of mania.

Angle-Closure Glaucoma
The pupillary dilation that occurs following use of many antidepressant drugs including duloxetine may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

Seizures
In reported adult placebo-controlled clinical trials, seizures/convulsions occurred in 0.02% of patients treated with duloxetine and 0.01% of patients treated with placebo. Duloxetine should be prescribed with care in patients with a history of a seizure disorder.

Effect on Blood Pressure
In reported adult placebo-controlled clinical trials across indications from baseline to endpoint, duloxetine treatment was associated with mean increases of 0.5 mm Hg in systolic blood pressure and 0.8 mm Hg in diastolic blood pressure compared to mean decreases of 0.6 mm Hg systolic and 0.3 mm Hg diastolic in placebo-treated patients. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure. Blood pressure should be measured prior to initiating treatment and periodically measured throughout treatment.

Hyponatremia
Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including duloxetine. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion. Cases with serum sodium lower than 110 mmol/L have been reported and appeared to be reversible when duloxetine was discontinued. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk. Discontinuation of duloxetine should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Use in Patients with Concomitant Illness
Clinical experience with duloxetine in patients with concomitant systemic illnesses is limited. There is no information on the effect that alterations in gastric motility may have on the stability of duloxetine's enteric coating. In extremely acidic conditions, duloxetine, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Caution is advised in using duloxetine in patients with conditions that may slow gastric emptying (e.g., some diabetics).

Hepatic Impairment
Avoid use in patients with chronic liver disease or cirrhosis.

Severe Renal Impairment

Avoid use in patients with severe renal impairment, glomerular filtration rate <30 mL/min. Increased plasma concentration of duloxetine, and especially of its metabolites, occur in patients with end-stage renal disease (requiring dialysis).

Glycemic Control in Patients with Diabetes

Duloxetine treatment worsens glycemic control in some patients with diabetes. In three reported clinical trials of duloxetine for the management of neuropathic pain, the mean duration of diabetes was approximately 12 years, the mean baseline fasting blood glucose was 176 mg/dL, and the mean baseline hemoglobin A1c (HbA1c) was 7.8%. In the 12-week acute treatment phase of these studies, duloxetine was associated with a small increase in mean fasting blood glucose as compared to placebo. In the extension phase of these studies, which lasted up to 52 weeks, mean fasting blood glucose increased by 12 mg/dL in the duloxetine group and decreased by 11.5 mg/dL in the routine care group. HbA1c increased by 0.5% in the duloxetine and by 0.2% in the routine care groups.

Urinary Hesitation and Retention

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. In post marketing experience, cases of urinary retention have been observed.

4.5 Drugs interactions

Pregabalin

Since pregabalin is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (less than 2% of a dose recovered in urine as metabolites), and does not bind to plasma proteins, its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions or protein binding displacement. *In vitro* and *in vivo* studies showed that pregabalin is unlikely to be involved in significant pharmacokinetic drug interactions. Specifically, there are no pharmacokinetic interactions between pregabalin and the following antiepileptic drugs: carbamazepine, valproic acid, lamotrigine, phenytoin, phenobarbital, and topiramate. Important pharmacokinetic interactions would also not be expected to occur between pregabalin and commonly used antiepileptic drugs.

Pharmacodynamics

Multiple oral doses of pregabalin were co-administered with oxycodone, lorazepam, or ethanol. Although no pharmacokinetic interactions were seen, additive effects on cognitive and gross motor functioning were seen when pregabalin was coadministered with these drugs. No clinically important effects on respiration were seen.

Duloxetine

Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

Inhibitors of CYP1A2

When duloxetine 60 mg was co-administered with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to male subjects (n=14) duloxetine AUC was increased approximately 6-fold, the Cmax was increased about 2.5-fold, and duloxetine t1/2 was increased approximately 3-fold. Other drugs that inhibit CYP1A2 metabolism include cimetidine and quinolone antimicrobials such as ciprofloxacin and enoxacin.

Inhibitors of CYP2D6

Concomitant use of duloxetine (40 mg once daily) with paroxetine (20 mg once daily) increased the concentration of duloxetine AUC by about 60%, and greater degrees of inhibition are expected with higher doses of paroxetine. Similar effects would be expected with other potent CYP2D6 inhibitors (e.g., fluoxetine, quinidine).

Dual Inhibition of CYP1A2 and CYP2D6

Concomitant administration of duloxetine 40 mg twice daily with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to CYP2D6 poor metabolizer subjects (n=14) resulted in a 6-fold increase in duloxetine AUC and Cmax.

Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin)

Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs or SNRIs are co-administered with warfarin. Patients receiving warfarin therapy should be carefully monitored when duloxetine is initiated or discontinued.

Lorazepam

Under steady-state conditions for duloxetine (60 mg Q 12 hours) and lorazepam (2 mg Q 12 hours), the pharmacokinetics of duloxetine were not affected by coadministration.

Temazepam

Under steady-state conditions for duloxetine (20 mg qhs) and temazepam (30 mg qhs), the pharmacokinetics of duloxetine were not affected by co-administration.

Drugs that Affect Gastric Acidity

Duloxetine has an enteric coating that resists dissolution until reaching a segment of the gastrointestinal tract where the pH exceeds 5.5. In extremely acidic conditions, duloxetine, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Caution is advised in using duloxetine in patients with conditions that may slow gastric emptying (e.g., some diabetics). Drugs that raise the gastrointestinal pH may lead to an earlier release of duloxetine. However, co-administration of duloxetine with aluminum- and magnesium-containing antacids (51 mEq) or duloxetine with famotidine, had no significant effect on the rate or extent of duloxetine absorption after administration of a 40 mg oral dose. It is unknown whether the concomitant administration of proton pump inhibitors affects duloxetine absorption.

Drugs Metabolized by CYP1A2

In vitro drug interaction studies demonstrate that duloxetine does not induce CYP1A2 activity. Therefore, an increase in the metabolism of CYP1A2 substrates (e.g., theophylline, caffeine) resulting from induction is not anticipated, although clinical studies of induction have not been performed. Duloxetine is an inhibitor of the CYP1A2 isoform in *in vitro* studies, and in two clinical studies the average (90% confidence interval) increase in theophylline AUC was 7% (1%-15%) and 20% (13%-27%) when co-administered with duloxetine (60 mg twice daily).

Drugs Metabolized by CYP2D6

Duloxetine is a moderate inhibitor of CYP2D6. When duloxetine was administered (at a dose of 60 mg twice daily) in conjunction with a single 50 mg dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold.

Drugs Metabolized by CYP2C9

Duloxetine does not inhibit the *in vitro* enzyme activity of CYP2C9. Inhibition of the metabolism of CYP2C9 substrates is therefore not anticipated, although clinical studies have not been performed.

Drugs Metabolized by CYP3A

Results of *in vitro* studies demonstrate that duloxetine does not inhibit or induce CYP3A activity. Therefore, an increase or decrease in the metabolism of CYP3A substrates (e.g., oral contraceptives and other steroidal agents) resulting from induction or inhibition is not anticipated, although clinical studies have not been performed.

Monoamine Oxidase Inhibitors

Monoamine Oxidase Inhibitors (MAOIs): The use of MAOIs intended to treat psychiatric disorders with duloxetine or within 5 days of stopping treatment with duloxetine is contraindicated because of an increased risk of serotonin syndrome. The use of duloxetine within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated. Starting duloxetine in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome.

Serotonergic Drugs

Based on the mechanism of action of SNRIs and SSRIs, including duloxetine, and the potential for serotonin syndrome, caution is advised when duloxetine is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort. The concomitant use of duloxetine with other SSRIs, SNRIs or tryptophan is not recommended.

Triptans

There have been rare post-marketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of duloxetine with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Alcohol

When duloxetine and ethanol were administered several hours apart so that peak concentrations of each would coincide, duloxetine did not increase the impairment of mental and motor skills caused by alcohol. In the reported duloxetine clinical trials database, three duloxetine-treated patients had liver injury as manifested by ALT and total bilirubin elevations, with evidence of obstruction. Substantial intercurrent ethanol use was present in each of these cases, and this may have contributed to the abnormalities seen.

CNS Drugs

Given the primary CNS effects of duloxetine, it should be used with caution when it is taken in combination with or substituted for other centrally acting drugs, including those with a similar mechanism of action.

Drugs Highly Bound to Plasma Protein

Because duloxetine is highly bound to plasma protein, administration of duloxetine to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse reactions.

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

Pregabalin

Women of childbearing potential/Contraception in males and females
As the potential risk for humans is unknown, effective contraception must be used in women of child bearing potential.

Pregnancy
There are no adequate data from the use of pregabalin in pregnant women.
Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.
Pregabalin and duloxetine should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the foetus).

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

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

Duloxetine

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

Pregnancy
There are no adequate data on the use of duloxetine in pregnant women. Studies in animals have shown reproductive toxicity at systemic exposure levels (AUC) of duloxetine lower than the maximum clinical exposure.
The potential risk for humans is unknown. 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. Pregabalin and 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.

Breast-Feeding
Duloxetine is very weakly excreted into human milk, based on a reported 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 pregabalin and duloxetine while breast-feeding is not recommended.

4.7 Effects on ability to drive and use machines

Combination of pregabalin and duloxetine may have minor or moderate influence on the ability to drive and use machines. Drug 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

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.

Below is the lists all adverse reactions, which 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).

Infections and infestations

Common: Nasopharyngitis

Blood and lymphatic system disorders

Uncommon: Neutropaenia

Immune system disorders

Uncommon: Hypersensitivity

Rare: Angioedema, allergic reaction

Metabolism and nutrition disorders

Common: Appetite increased

Uncommon: Anorexia, hypoglycaemia

Psychiatric disorders

Common: Euphoric mood, confusion, irritability, disorientation, insomnia, libido decreased

Uncommon: Hallucination, panic attack, restlessness, agitation, depression, depressed mood, elevated mood, aggression, mood swings, depersonalisation, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy

Rare: Disinhibition

Nervous system disorders

Very Common: Dizziness, somnolence, headache

Common: Ataxia, coordination abnormal, tremor, dysarthria, amnesia, memory impairment, disturbance in attention, paraesthesia, hypoaesthesia, sedation, balance disorder, lethargy

Uncommon: Syncope, stupor, myoclonus, loss of consciousness, psychomotor hyperactivity, dyskinesia, dizziness postural, intention tremor, nystagmus, cognitive disorder, mental impairment, speech disorder, hyporeflexia, hyperaesthesia, burning sensation, ageusia, malaise

Rare: Convulsions, parosmia, hypokinesia, dysgraphia

Eye disorders

Common: Vision blurred, diplopia

Uncommon: Peripheral vision loss, visual disturbance, eye swelling, visual field defect, visual acuity reduced, eye pain, asthenopia, photopsia, dry eye, lacrimation increased, eye irritation

Rare: Vision loss, keratitis, oscillopsia, altered visual depth perception, mydriasis, strabismus, visual brightness

Ear and labyrinth disorders

Common: Vertigo

Uncommon: Hyperacusis

Cardiac disorders

Uncommon: Tachycardia, atrioventricular block first degree, sinus bradycardia, congestive heart failure

Rare: QT prolongation, sinus tachycardia, sinus arrhythmia

Vascular disorders

Uncommon: Hypotension, hypertension, hot flushes, flushing, peripheral coldness

Respiratory, thoracic and mediastinal disorders

Uncommon: Dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness

Rare: Pulmonary oedema, throat tightness

Gastrointestinal disorders

Common: Vomiting, nausea, constipation, diarrhoea, flatulence, abdominal distension, dry

mouth

Uncommon: Gastrooesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral

Rare: Ascites, pancreatitis, swollen tongue, dysphagia

Hepatobiliary disorders

Uncommon: Elevated liver enzymes*

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.

Rare: Jaundice

Very rare: Hepatic failure, hepatitis

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, blood glucose increased, platelet count

decreased, blood creatinine increased, blood potassium decreased, weight decreased

Rare: White blood cell count decreased

Duloxetine

The most commonly reported adverse reactions in patients treated with duloxetine 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.

Infections and infestations

Uncommon: Laryngitis

Immune system disorders

Rare: Anaphylactic reaction, Hypersensitivity disorder

Endocrine disorders

Rare: Hypothyroidism

Metabolism and nutrition disorders

Common: Decreased appetite

Uncommon: Hyperglycaemia (reported especially in diabetic patients)

Rare: Dehydration, Hyponatraemia, SIADH

Psychiatric disorders

Common: Insomnia, Agitation, Libido decreased, Anxiety, Orgasm abnormal, Abnormal dreams

Uncommon: Suicidal ideation, Sleep disorder, Bruxism, Disorientation, Apathy

Rare: Suicidal behaviour, Mania, Hallucinations, Aggression and anger

Nervous system disorders

Very common: Headache, Somnolence

Common: Dizziness, Lethargy, Tremor, Paraesthesia

Uncommon: Myoclonus, Akathisia, Nervousness, Disturbance in attention, Dysgeusia, Dyskinesia, Restless legs syndrome, Poor quality sleep

Rare: Serotonin syndrome, Convulsion, Psychomotor restlessness, Extra-pyramidal symptoms

Eye disorders

Common: Blurred vision

Uncommon: Mydriasis, Visual impairment

Rare: Glaucoma

Ear and labyrinth disorders

Common: Tinnitus

Uncommon: Vertigo, Ear pain

Cardiac disorders

Common: Palpitations

Uncommon: Tachycardia, Supraventricular arrhythmia, mainly atrial fibrillation

Vascular disorders

Common: Blood pressure increase, Flushing, Peripheral coldness

Uncommon: Syncope, Hypertension, Orthostatic hypotension

Rare: Hypertensive crisis

Respiratory, thoracic and mediastinal disorders

Common: Yawning

Uncommon: Throat tightness Epistaxis

Rare: Interstitial lung disease, Eosinophilic pneumonia

Gastrointestinal disorders

Very common: Nausea, Dry mouth

Common: Constipation, Diarrhoea, Abdominal pain, Vomiting, Dyspepsia, Flatulence

Uncommon: Gastrointestinal haemorrhage, Gastroenteritis, Eructation, Gastritis, Dysphagia

Rare: Stomatitis, Haematochezia, Breath odour, Microscopic colitis

Hepato-biliary disorders

Uncommon: Hepatitis, Elevated liver enzymes, (ALT, AST, alkaline phosphatase), Acute liver injury

Rare: Hepatic failure, Jaundice

Skin and subcutaneous tissue disorders

Common: Sweating increased, Rash

Uncommon: Night sweats, Urticaria, Dermatitis contact, Cold sweat, Photosensitivity reactions, Increased tendency to bruise

Rare: Stevens-Johnson Syndrome, Angioneurotic oedema

Very rare: Cutaneous vasculitis

Musculoskeletal and connective tissue disorders

Common: Musculoskeletal pain, Muscle spasm

Uncommon: Muscle tightness, Muscle twitching

Rare: Trismus

Renal and urinary disorders

Common: Dysuria, Pollakiuria

Uncommon: Urinary retention, Urinary hesitation, Nocturia, Polyuria, Urine flow decreased

Rare: Urine odour abnormal

Reproductive system and breast disorders

Common: Erectile dysfunction, Ejaculation disorder, Ejaculation delayed

Uncommon: Gynaecological haemorrhage, Menstrual disorder, Sexual dysfunction, Testicular pain

Rare: Menopausal symptoms, Galactorrhoea, Hyperprolactinaemia, Postpartum haemorrhage

General disorders and administration site conditions

Common: Falls, Fatigue

Uncommon Chest pain, Feeling abnormal, Feeling cold, Thirst, Chills, Malaise, Feeling hot, Gait disturbance

Investigations

Common: Weight decrease

Uncommon: Weight increase, Blood creatine phosphokinase increased, Blood potassium increased

Rare: Blood cholesterol increased

Reporting of side effects

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

4.9 Overdose

Pregabalin

In the 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.

5 Pharmacological Properties

5.1 Mechanism of Action

Pregabalin

Pregabalin binds to an auxiliary subunit (α -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.

5.2 Pharmacodynamic Properties

Pregabalin

Pregabalin binds with high affinity to the alpha2-delta site (an auxiliary subunit of voltage-gated calcium channels) in central nervous system tissues. Although the mechanism of action of pregabalin has not been fully elucidated, results with genetically modified mice and with compounds structurally related to pregabalin (such as gabapentin) suggest that binding to the alpha2-delta subunit may be involved in pregabalin's anti-nociceptive and anti-seizure effects in animals. In animal models of nerve damage, pregabalin has been shown to reduce calcium dependent release of pro-nociceptive neurotransmitters in the spinal cord, possibly by disrupting alpha2-delta containing-calcium channel trafficking and/or reducing calcium currents. Evidence from other animal models of nerve damage and persistent pain suggest the anti-nociceptive activities of pregabalin may also be mediated through interactions with descending noradrenergic and serotonergic pathways originating from the brainstem that modulate pain transmission in the spinal cord.

While pregabalin is a structural derivative of the inhibitory neurotransmitter GABA, it does not bind directly to GABAA, GABAB, or benzodiazepine receptors, does not augment GABAA responses in cultured neurons, does not alter rat brain GABA concentration or have acute effects on GABA uptake or degradation. However, in cultured neurons prolonged application of Pregabalin increases the density of GABA transporter protein and increases the rate of functional GABA transport. Pregabalin does not block sodium channels, is not active at opiate receptors, and does not alter cyclooxygenase enzyme activity. It is inactive at serotonin and dopamine receptors and does not inhibit dopamine, serotonin, or noradrenaline reuptake.

Duloxetine

Preclinical 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. Duloxetine belongs to a class of drugs, which is 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.

Pregabalin and Duloxetine Combination

Pregabalin and duloxetine combination has been previously studied for its efficacy and tolerability in diabetic peripheral neuropathic pain. The reported study was a randomized

control trial (COMBO-DN study) where pregabalin (300 mg/day) and duloxetine (60 mg/day) combination was administered to patients. Combination therapy was considered to be effective, safe, and well tolerated when administered to patients with diabetic peripheral neuropathic pain. TEAEs were comparable between high-dose monotherapy (pregabalin 600mg/day and duloxetine 120mg/day) and combination treatment, and safety and tolerability were not impacted negatively when 300 mg/day pregabalin and 60 mg/day duloxetine were combined. Adverse events which were reported are dizziness, nausea, pain in extremity, somnolence, vomiting, diarrhea, headache, hypoglycaemia and weight increase (Pain, 154 (2013) 2616–2625).

Pregabalin and Duloxetine Fix Dose Combination

In a reported phase III randomized, multi-centric study conducted by Torrent Pharmaceuticals Ltd., fixed dose combination of pregabalin and duloxetine capsule was compared to monotherapy of pregabalin upon 7 weeks of treatment. The study was conducted with 328 subjects with neuropathic pain. The individual dose of pregabalin in the fixed dose combination (50 mg pregabalin + 20 mg duloxetine, 75 mg pregabalin + 20 mg duloxetine, and 75 mg pregabalin + 30 mg duloxetine) was lower than pregabalin monotherapy doses (75 mg, 100 mg, 150 mg). It was observed that similar relief in neuropathic pain was reported when pregabalin and duloxetine fix dose combination compared with higher dose pregabalin administered alone. The study demonstrated that fix dose combination of pregabalin and duloxetine (50 mg + 20 mg, 75 mg + 20 mg, 75 mg + 30 mg) was non-inferior in relieving neuropathic pain when pregabalin was administered as monotherapy at a higher doses (75 mg, 100 mg, 150 mg). Pain intensity was measured using 11-point (0 to 10) Numeric Pain Rating Scale (NPRS) in this study.

Non-Inferiority Analysis of Mean Change in NPRS Score from Baseline to Week 7 (Day 49) EOT - mITT Population

Variable	Statistic	Test (N = 158)	Reference (N = 157)
Mean CFB to Visit 7 EOT (Day 49 ± 4)	Mean ± SD	-4.49 ± 1.669	-4.66 ± 1.496
	Difference (Test - Referenc	0.17	
	95% CI	(-0.18, 0.52)	

Treatment Specifications: Test = Fixed dose combination of pregabalin and duloxetine capsule; Reference = Pregabalin capsule.
Abbreviation(s): CFB = Change from baseline; CI = Confidence interval; EOT = End of the treatment; mITT =Modified intent to treat; N =Number of subjects in specified treatment; NPRS=Numeric pain rating scale; SD = Standard deviation.
Note 1: CFB = post baseline value – baseline value.

Secondary Efficacy Endpoints:

Results of mITT population are summarized below:

Mean change in numeric pain rating scale from baseline to Week 2, 3 and 5

The mean change in NPRS score from baseline to Week 2, 3 and 5 was -2.49, -3.19 and -3.89, respectively with the pregabalin and duloxetine fix dose combination treatment and -2.65, -

3.34 and -4.03, respectively with pregabalin monotherapy. No statistically significant difference was observed between the two treatment groups with regards to mean change in NPRS score from baseline to Week 2, 3 and 5 ($p>0.05$).

Proportion of responders (≥30% & ≥50% improvement in pain (NPRS) from baseline) at end of the treatment (Week 7)

The proportion of subjects achieving a ≥ 30% *& ≥50%* improvement in pain (NPRS) at Week 7 was 96.20% & 84.18% with the pregabalin and duloxetine fix dose combination treatment and 98.73% & 89.17% with the pregabalin monotherapy. No statistically significant difference was observed between the two treatment groups with regards to proportion of responders at Week 7 ($p>0.05$).

Mean change in NPSI score from baseline to Week 7; percentage of subjects who required rescue medication for inadequate pain relief with study drugs; patient global impression of improvement (PGI-I) at end of the treatment and clinical global impression of improvement (CGI-I) at end of the treatment was found similar with no statistically significant difference between pregabalin and duloxetine fix dose combination and pregabalin monotherapy treatment group.

Incidence of treatment emergent adverse events [dizziness, somnolence and/or peripheral edema] in test arm against reference arm.

Incidence of dizziness and somnolence was comparable between the two treatment groups. Incidence of peripheral edema was higher with the pregabalin and duloxetine fix dose combination treatment (3.11%) as compared to the pregabalin monotherapy treatment (0%) although statistically not significant ($p>0.05$).
Results obtained in the mITT population were supported by those seen in the PP population for all the secondary efficacy endpoints.

Adverse events:

No SAE was reported during the reported study.

A total of 88 Treatment Emergent Adverse Events (TEAEs) were reported in 59 subjects (36.65%) receiving pregabalin and duloxetine fix dose combination treatment, and 73 TEAEs were reported in 56 subjects (34.78%) receiving the pregabalin monotherapy treatment. Most of the reported TEAEs were of mild severity. Overall, the percentage of subjects who experienced TEAEs was comparable between the two treatment groups.

Discontinue due to TEAEs:

Two subjects, one with reported erythema and other with sedation were discontinued from the pregabalin monotherapy treatment group due to TEAE. No subject was discontinued due to TEAE in the pregabalin and duloxetine fix dose combination treatment group.

Incidence of TEAEs:

Incidence of somnolence and dizziness was highest as compared to other TEAEs. Among the reported TEAEs, incidence of edema was higher in the pregabalin monotherapy treatment

group (4.35%) as compared to test treatment group (0.62%). Incidence of other TEAEs was comparable between the two groups.

TEAEs with Causality:

Most of the TEAEs were at least possibly related to the reported study treatment.

TEAEs with Severity:

One severe TEAE (back pain) was reported in one subject (0.62%) receiving the pregabalin monotherapy treatment. A total of 6 TEAEs (Two incidences of somnolence and one incidence of diarrhea, headache, thermal burn and dizziness each) with moderate severity were reported in 4 subjects (2.48%) receiving the pregabalin and duloxetine fix dose combination treatment. A total of 9 TEAEs (three incidences of peripheral edema and one incidence of fatigue, back pain, edema, dizziness, sedation and vertigo each) with moderate severity were reported in 08 subjects (4.97%) receiving the pregabalin monotherapy treatment. Rest TEAEs were of mild severity.

Vital Signs, Physical Findings and Other Observation Related to Safety:

Mean values of each vital signs (blood pressure, pulse rate, respiratory rate and oral temperature) were comparable between the two treatment groups. One subject (0.62%) in each treatment group reported pyrexia. For the rest of all the subjects, vital signs were within clinically acceptable limits.
No clinically significant findings were observed during the physical examination and 12-Lead ECG.
Based on an assessment of the AEs, physical examination, vital sign measurements, and 12-Lead ECGs, both the treatments were considered as comparable, safe and well tolerated.

5.3 Pharmacokinetic Properties

Pregabalin

Absorption

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

Distribution

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

Biotransformation

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

Reported 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.

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.

Duloxetine

Duloxetine is extensively metabolised by oxidative enzymes (CYP1A2 and the polymorphic CYP2D6), followed by conjugation. The pharmacokinetics of duloxetine demonstrate large intersubjective variability (generally 50-60%), partly due to gender, age, smoking status, and CYP2D6 metaboliser status.

Absorption

Duloxetine is well absorbed after oral administration, with a C_{max} occurring 6 hours' post-dose. The absolute oral bioavailability of duloxetine ranged from 32% to 80% (mean of 50%). Food delays the time to reach the peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (approximately 11%). These changes do not have any clinical significance.

Distribution

Duloxetine is approximately 96% bound to human plasma proteins. Duloxetine binds to both albumin and $alpha_1$-acid glycoprotein. Protein binding is not affected by renal or hepatic impairment.

Biotransformation

Duloxetine is extensively metabolised and the metabolites are excreted principally in urine. Both cytochromes P450-2D6 and 1A2 catalyse the formation of the two major metabolites, glucuronide conjugate of 4-hydroxy duloxetine and sulfate conjugate of 5-hydroxy, 6-methoxy duloxetine. Based upon *in vitro* studies, the circulating metabolites of duloxetine are considered pharmacologically inactive. The pharmacokinetics of duloxetine in patients who are poor metabolisers with respect to CYP2D6 has not been specifically investigated. Limited data suggest that the plasma levels of duloxetine are higher in these patients.

Elimination

The elimination half-life of duloxetine ranges from 8 to 17 hours (mean of 12 hours). After an intravenous dose the plasma clearance of duloxetine ranges from 22 l/hr to 46 l/hr (mean of 36 l/hr). After an oral dose the apparent plasma clearance of duloxetine ranges from 33 to 261 l/hr (mean 101 l/hr).

Gender

Pharmacokinetic differences have been identified between males and females (apparent plasma clearance is approximately 50% lower in females). Based upon the overlap in the range of clearance, gender-based pharmacokinetic differences do not justify the recommendation for using a lower dose for female patients.

Age

Pharmacokinetic differences have been identified between younger and elderly females (≥65 years) (AUC increases by about 25% and half-life is about 25% longer in the elderly), although the magnitude of these changes is not sufficient to justify adjustments to the dose. As a general recommendation, caution should be exercised when treating the elderly.

Renal impairment

End stage renal disease (ESRD) patients receiving dialysis had 2-fold higher duloxetine C_{max} and AUC values compared with healthy subjects. Pharmacokinetic data on duloxetine is limited in patients with mild or moderate renal impairment.

Hepatic impairment

Moderate liver disease (Child-Pugh Class B) affected the pharmacokinetics of duloxetine. Compared with healthy subjects, the apparent plasma clearance of duloxetine was 79% lower, the apparent terminal half-life was 2.3-times longer, and the AUC was 3.7-times higher in patients with moderate liver disease. The pharmacokinetics of duloxetine and its metabolites have not been studied in patients with mild or severe hepatic insufficiency.

Breast-feeding mothers

The disposition of duloxetine was studied in 6 lactating women who were at least 12-weeks postpartum. Duloxetine is detected in breast milk, and steady-state concentrations in breast milk are about one-fourth those in plasma. The amount of duloxetine in breast milk is approximately 7µg/day while on 40 mg twice-daily dosing. Lactation did not influence duloxetine pharmacokinetics.

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

Duloxetine was not genotoxic in a standard battery of tests and was not carcinogenic in rats.

Multinucleated cells were seen in the liver in the absence of other histopathological changes in the reported rat carcinogenicity study. The underlying mechanism and the clinical relevance are unknown. Female mice receiving duloxetine for 2 years had an increased incidence of hepatocellular adenomas and carcinomas at the high dose only (144 mg/kg/day), but these were considered to be secondary to hepatic microsomal enzyme induction. The relevance of this mouse data to humans is unknown. Female rats receiving duloxetine (45 mg/kg/day) before and during mating and early pregnancy had a decrease in maternal food consumption and body weight, oestrous cycle disruption, decreased live birth indices and progeny survival, and progeny growth retardation at systemic exposure levels estimated to be at the most at maximum clinical exposure (AUC). In a reported embryotoxicity study in the rabbit, a higher incidence of cardiovascular and skeletal malformations was observed at systemic exposure levels below the maximum clinical exposure (AUC). No malformations were observed in another reported study testing a higher dose of a different salt of duloxetine. In prenatal/postnatal toxicity studies in the rat, duloxetine induced adverse behavioural effects in the offspring at exposures below maximum clinical exposure (AUC).

Studies in juvenile rats reveal transient effects on neurobehaviour, as well as significantly decreased body weight and food consumption; hepatic enzyme induction; and hepatocellular vacuolation at 45 mg/kg/day. The general toxicity profile of duloxetine in juvenile rats was similar to that in adult rats. The no-adverse effect level was determined to be 20 mg/kg/day.

7. DESCRIPTION

PREGEB D/ PREGABA-D/ PREGALIN D (50 mg + 20 mg)

Size ‘2’, hard gelatin capsule having orange opaque cap and white opaque body, imprinted with “50+20” on the body with black ink, containing white to off-white powder and off white to reddish brown colored pellets.

PREGEB D/ PREGABA-D/ PREGALIN D (75 mg + 20 mg)

Size ‘1’, hard gelatin capsule having yellow opaque cap and white opaque body, imprinted with “75+20” on the body with black ink, containing white to off-white powder and off white to reddish brown colored pellets.

PREGEB D/ PREGABA-D/ PREGALIN D (75 mg + 30 mg)

Size ‘1’, hard gelatin capsule having blue opaque cap and white opaque body, imprinted with “75+30” on the body with black ink, containing white to off-white powder and off white to reddish brown colored pellets.

8. PHARMACEUTICAL PARTICULAR

8.1 Incompatibilities

Not available.

8.2 Shelf-life

Do not use later than expiry date.

8.3 Packaging information

PREGEB D/ PREGABA-D/ PREGALIN D is available in blister strips of 10 capsules.

8.4 Storage and Handing Instructions

Store at temperature not exceeding 30°C, protected from light and moisture.

9. PATIENT COUNSELLING INFORMATION

Package leaflet: Information for the user

PREGEB D/ PREGABA-D/ PREGALIN D
Pregabalin and Duloxetine 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.

What is in this leaflet?

9.1 What PREGEB D/ PREGABA-D/ PREGALIN D is and what it is used for?
9.2 What you need to know before you take PREGEB D/ PREGABA-D/ PREGALIN D?
9.3 How to take PREGEB D/ PREGABA-D/ PREGALIN D?
9.4 Possible side effects?
9.5 How to store PREGEB D/ PREGABA-D/ PREGALIN D?
9.6 Contents of the pack and other information.

9.1 What PREGEB D/ PREGABA-D/ PREGALIN D is and what it is used for?

Drug is fix dose combination of pregabalin and duloxetine and this medicine is used to treat neuropathic pain.

9.2 What you need to know before you take PREGEB D/ PREGABA-D/ PREGALIN D?

Do not take PREGEB D/ PREGABA-D/ PREGALIN D if you:

- are allergic to pregabalin or duloxetine or any of the other ingredients of this medicine.
- have liver disease.
- have severe kidney disease.
- are taking or have taken within the last 14 days, another medicine known as a monoamine oxidase inhibitor (MAOI).
- are taking fluvoxamine which is usually used to treat depression, ciprofloxacin or enoxacin which are used to treat some infections.
- are taking other medicines containing duloxetine.

Talk to your doctor if you have high blood pressure or heart disease. Your doctor will tell you if you should be taking pregabalin and duloxetine containing drug.

Warnings and precautions

Talk to your doctor or pharmacist before taking pregabalin and duloxetine.

- Some patients taking pregabalin and duloxetine 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.
- Pregabalin and duloxetine 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.
- Pregabalin and duloxetine 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 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.
- There have been reports of heart failure in some patients when taking Pregabalin and Duloxetine; 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 pregabalin and Duloxetine. If while taking pregabalin and duloxetine you notice decreased urination, you should tell your doctor as stopping the medicine may improve this.
- A small number of people being treated pregabalin and duloxetine have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.
- When pregabalin and duloxetine 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 pregabalin and duloxetine or shortly after stopping pregabalin and duloxetine. If you experience a convulsion, contact your doctor immediately.
- There have been reports of reduction in brain function (encephalopathy) in some patients taking pregabalin and duloxetine when they have other conditions. Tell your doctor if you have a history of any serious medical conditions, including liver or kidney disease.
- are taking other medicines to treat depression (see 'Other medicines and Pregabalin and Duloxetine')
- are taking St. John's Wort, a herbal treatment (Hypericum perforatum)
- have kidney disease
- have had seizures (fits)
- have had mania
- suffer from bipolar disorder
- have eye problems, such as certain kinds of glaucoma (increased pressure in the eye)
- have a history of bleeding disorders (tendency to develop bruises)
- are at risk of low sodium levels (for example if you are taking diuretics, especially if you are elderly)
- are currently being treated with another medicine which may cause liver damage
- are taking other medicines containing duloxetine (see 'Other medicines and Pregabalin and Duloxetine')

Pregabalin and duloxetine may cause a sensation of restlessness or an inability to sit or stand still. You should tell you doctor if this happens to you**.**

Medicines like pregabalin and duloxetine (so called SSRIs/SNRIs) may cause symptoms of sexual dysfunction. In some cases, these symptoms have continued after stopping treatment.

Thoughts of suicide and worsening of your depression or anxiety disorder
If you are depressed and/or have anxiety disorders, you can sometimes have thoughts of harming or killing yourself.

You may be more likely to think like this if you:
- have previously had thoughts about killing or harming yourself are a young adult. Information from reported clinical trials has shown an increased risk of suicidal behaviour in adults aged less than 25 years with psychiatric conditions who were treated with pregabalin and duloxetine.

If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital straight away.
You may find it helpful to tell a relative or close friend that you are depressed or have an anxiety disorder, and ask them to read this leaflet. You might ask them to tell you if they think your depression or anxiety is getting worse, or if they are worried about changes in your behaviour.

Children and adolescents:
The safety and efficacy in children and adolescents (under 18 years of age) has not been established and therefore, pregabalin and duloxetine should normally not be used for children and adolescents under 18 years. Also, you should know that patients under 18 have an increased risk of side-effects such as suicide attempt, suicidal thoughts and hostility

(predominantly aggression, oppositional behaviour and anger) when they take this class of medicines. Despite this, your doctor may prescribe pregabalin and duloxetine for patients under 18 because he/she decides that this is in their best interests. If your doctor has prescribed pregabalin and duloxetine for a patient under 18 and you want to discuss this, please go back to your doctor. You should inform your doctor if any of the symptoms listed above develop or worsen when patients under 18 are taking pregabalin and duloxetine.

Other medicines and pregabalin and duloxetine:
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Your doctor should decide whether you can take pregabalin and duloxetine with other medicines. Do not start or stop taking any medicines, including those bought without a prescription and herbal remedies, before checking with your doctor.

You should also tell your doctor if you are taking any of the following:

Monoamine oxidase inhibitors (MAOIs):
You should not take pregabalin and duloxetine if you are taking, or have recently taken (within the last 14 days) another antidepressant medicine called a monoamine oxidase inhibitor (MAOI). Examples of MAOIs include moclobemide (an antidepressant) and linezolid (an antibiotic). Taking a MAOI together with many prescription medicines, including pregabalin and duloxetine, can cause serious or even life-threatening side effects. You must wait at least 14 days after you have stopped taking an MAOI before you can take pregabalin and duloxetine. Also, you need to wait at least 5 days after you stop taking pregabalin and duloxetine before you take a MAOI.

Medicines that cause sleepiness:
These include medicines prescribed by your doctor including benzodiazepines, strong painkillers, antipsychotics, phenobarbital and antihistamines.

Medicines that increase the level of serotonin:
Triptans, tramadol, tryptophan, SSRIs (such as paroxetine and fluoxetine), SNRIs (such as venlafaxine), tricyclic antidepressants (such as clomipramine, amitriptyline), pethidine, St John's Wort and MAOIs (such as moclobemide and linezolid). These medicines increase the risk of side effects; if you get any unusual symptom taking any of these medicines together with pregabalin and duloxetine, you should see your doctor.

Oral anticoagulants or antiplatelet agents:
Medicines which thin the blood or prevent the blood from clotting. These medicines might increase the risk of bleeding.

Pregabalin and duloxetine with food, drink and alcohol
Pregabalin and duloxetine may be taken with or without food. Care should be taken if you drink alcohol while you are being treated with pregabalin and duloxetine. It is advised not to drink alcohol while taking pregabalin and duloxetine.

Pregabalin and duloxetine and certain other medicines may influence each other (interaction). When taken with certain other medicines, pregabalin and duloxetine may potentiate the side effects seen with these medicines, including respiratory failure and coma.

The degree of dizziness, sleepiness and decreased concentration may be increased if pregabalin and duloxetine is taken together with medicines containing:

- Oxycodone – (used as a pain-killer)
- Lorazepam – (used for treating anxiety)
- Alcohol
- Pregabalin and duloxetine may be taken with oral contraceptives.

Pregnancy and breast-feeding

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

Tell your doctor if you become pregnant, or you are trying to become pregnant, while you are taking pregabalin and duloxetine. You should use pregabalin and duloxetine only after discussing the potential benefits and any potential risks to your unborn child with your doctor.

Make sure your midwife and/or doctor knows you are on pregabalin and duloxetine. When taken during pregnancy, similar drugs (SSRIs) may increase the risk of a serious condition in babies, called persistent pulmonary hypertension of the newborn (PPHN), making the baby breathe faster and appear bluish. These symptoms usually begin during the first 24 hours after the baby is born. If this happens to your baby, you should contact your midwife and/or doctor immediately.

Tell your doctor if you are breast-feeding. The use of pregabalin and duloxetine while breastfeeding is not recommended. You should ask your doctor or pharmacist for advice.

Driving and using machines

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

9.3 How to take PREGEB D/ PREGABA-D/ PREGALIN D

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure. Pregabalin and duloxetine is for oral use. You should swallow your capsule whole with a drink of water. Take the number of capsules as instructed by your doctor.

To help you remember to take pregabalin and duloxetine, you may find it easier to take it at the same times every day.

Talk with your doctor about how long you should keep taking pregabalin and duloxetine. Do not stop taking pregabalin and duloxetine, or change your dose, without talking to your doctor. Treating your disorder properly is important to help you get better. If it is not treated, your condition may not go away and may become more serious and difficult to treat.

If you take more PREGEB D/ PREGABA-D/ PREGALIN D than you should:

Call your doctor or pharmacist immediately if you take more than the amount of pregabalin and duloxetine prescribed by your doctor. You may feel sleepy, confused, agitated, or restless as a result of taking more PREGEB D/ PREGABA-D/ PREGALIN D than you should. Fits have also been reported. Symptoms of overdose include sleepiness, coma, serotonin syndrome (a rare reaction which may cause feelings of great happiness, drowsiness, clumsiness, restlessness, feeling of being drunk, fever, sweating or rigid muscles), fits, vomiting and fast heart rate.

If you forget to take PREGEB D/ PREGABA-D/ PREGALIN D:
It is important to take your pregabalin and duloxetine 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 D/ PREGABA-D/ PREGALIN D:
Do not stop taking pregabalin and duloxetine unless your doctor tells you to.

After stopping long and short-term pregabalin and duloxetine treatment, you need to know that you may experience certain side effects. These include, trouble sleeping, tingling feelings like pins and needles or electric shock-like feelings (particularly in the head), headache, nausea, feeling anxious, diarrhoea, flulike symptoms, convulsions, nervousness, depression, pain, sweating, fatigue, and dizziness. These symptoms may occur more commonly or severely if you have been taking pregabalin and duloxetine 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. These effects are normally mild to moderate and often disappear after a few weeks. The most common side effects (may affect more than 1 in 10 people) includes headache, feeling sleepy, dizziness, drowsiness, feeling sick (nausea) and dry mouth. Common side effects (may affect up to 1 in 10 people) includes lack of appetite, trouble sleeping, feeling agitated, less sex drive, anxiety, difficulty or failure to experience, muscle cramp, joint pain, back pain, pain in limb, feeling drunk, abnormal style of walking, orgasm, unusual dreams, dizziness, feeling sluggish, tremor, numbness, including numbness, pricking or tingling of the skin, disturbance in attention, clumsiness, memory impairment, loss of memory, tremor, difficulty with speaking, tingling feeling, numbness, sedation, lethargy, insomnia, fatigue, feeling abnormal, vertigo, problems with balance, fall, blurred eyesight, tinnitus (hearing sound in the ear when there is no external sound), feeling the heart pumping in the chest, increased blood pressure, flushing, increased yawning, constipation, diarrhoea, stomach pain, being sick (vomiting), heartburn or indigestion, breaking wind, dry mouth, nausea, swollen abdomen , increased sweating, (itchy) rash, muscle pain, muscle spasm, painful urination, frequent urination, problems getting an erection, changes in ejaculation, falls (mostly in elderly people), fatigue, sore throat, weight loss, weight gain.

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

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

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

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

9.5 How to store PREGEB D/ PREGABA-D/ PREGALIN D

Store at temperature not exceeding 30°C, protected from light and moisture.

9.6 Contents of the pack and other information

PREGEB D/ PREGABA-D/ PREGALIN D contains PREGABALIN in the strength of 50 mg/75 mg AND DULOXETINE in the strength of 20 mg/30 mg, as active ingredients.
The other ingredients are:

PREGEB D/ PREGABA-D/ PREGALIN D (50mg+20mg)

Starch, Talc, Sugar Spheres, Hypromellose, Sucrose, Hypromellose Acetate Succinate, Triethyl citrate, Polyethylene glycol 400 and Titanium dioxide SIZE "2" hard gelatin capsule.

PREGEB D/ PREGABA-D/ PREGALIN D (75mg+20mg)

Starch, Talc, Sugar Spheres, Hypromellose, Sucrose, Hypromellose Acetate Succinate, Triethyl citrate, Polyethylene glycol 400 and Titanium dioxide SIZE "1" hard gelatin capsule.

PREGEB D/ PREGABA-D/ PREGALIN D (75mg+30mg)

Starch, Talc, Sugar Spheres, Hypromellose, Sucrose, Hypromellose Acetate Succinate, Triethyl citrate, Polyethylene glycol 400 and Titanium dioxide SIZE "1" hard gelatin capsule.

What PREGEB D/ PREGABA-D/ PREGALIN D looks like and contents of the pack

PREGEB D/ PREGABA-D/ PREGALIN D is available in blister pack of 10 capsules.

10. DETAILS OF MANUFACTURER

Manufactured by:
Torrent Pharmaceuticals Ltd
Vill. Bhud & Makhnu Majra,
Teh. Baddi – 173 205, Dist. Solan (H.P.),
INDIA

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

MNB/05/183 issued on 27.10.2021

12. DATE OF REVISION

Not Applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/PREGEB D/ PREGABA-D/ PREGALIN D 75,50,20,30 mg/Oct21/01/PI