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

PREGEB NT

1. Generic Name

Pregabalin and Nortriptyline Tablets

2. Qualitative and quantitative composition

Each film-coated tablet contains:

Pregabalin I.P. ……. 75 mg

Nortriptyline Hydrochloride I.P

Equivalent to Nortriptyline……10 mg

Colours: Yellow Oxide of Iron and Titanium Dioxide I.P.

The excipients used are Microcrystalline Cellulose, Sodium Starch Glycolate, Mannitol, Polyvinyl Pyrrolidone, Isopropyl Alcohol, Disodium Edetate, Starch, Magnesium Stearate, Colloidal Silicon Dioxide, Udomix-521, Opadry II 85F190000, Yellow Oxide of Iron and Titanium Dioxide.

3. Dosage form and strength

Dosage form: Film coated tablet

Strength: Pregabalin 75 mg and Nortriptyline10 mg

4. Clinical Particulars

4.1 Therapeutic Indication

Indicated for treatment of diabetic neuropathy, post-herpetic neuralgia and fibromyalgia.

4.2 Posology and Method of Administration

Posology

Adults: Dosage should begin at a low level and be increased as required. Alternatively, the total daily dose may be given once a day. Plasma levels of nortriptyline should be monitored and maintained in the optimum range of 50 to 150 ng/ml.

Elderly and Adolescents:

Lower than usual dosages are recommended for elderly patients and adolescents. Lower dosages are also recommended for outpatients than for hospitalised patients who will be under close supervision. The physician should initiate dosage at a low level and increase it gradually, noting carefully the clinical response and any evidence of intolerance. Following remission, maintenance medication may be required for a longer period of time at the lowest dose that will maintain remission. If a patient develops minor side-effects, the dosage should be reduced. The

drug should be discontinued promptly if adverse effects of a serious nature or allergic manifestations occur.

Plasma levels: Optimal responses to nortriptyline have been associated with plasma concentrations of 50 to 150 ng/ml. Higher concentrations may be associated with more adverse experiences. Plasma concentrations are difficult to measure, and physicians should consult the laboratory professional staff.

Many antidepressants (tricyclic antidepressants, including nortriptyline, selective serotonin re-uptake inhibitors and others) are metabolised by the hepatic cytochrome P450 isoenzyme P450IID6. Three to ten per cent of the population have reduced isoenzyme activity ('poor metabolisers') and may have higher than expected plasma concentrations at usual doses. The percentage of 'poor metabolisers' in a population is also affected by its ethnic origin.

Older patients have been reported to have higher plasma concentrations of the active nortriptyline metabolite 10-hydroxynortriptyline. In one case, this was associated with apparent cardiotoxicity, despite the fact that nortriptyline concentrations were within the 'therapeutic range'. Clinical findings should predominate over plasma concentrations as primary determinants of dosage changes.

Neuropathic pain

PREGEB NT 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.

Method of administration

One tablet once daily or as directed by physician. Kindly follow physician’s advice

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Recent myocardial infarction, any degree of heart block or other cardiac arrhythmias.
- Severe liver disease.
- Mania.
- Nortriptyline is contra-indicated for the nursing mother and for children under the age of six years.

4.4 Special Warnings and Precautions for Use

Pregabalin

Diabetic patients

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

Hypersensitivity reactions

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

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

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

Vision-related effects

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

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

Renal failure

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

Withdrawal of concomitant anti-epileptic medicinal products

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

Withdrawal symptoms

After discontinuation of short-term and long-term treatment with pregabalin, withdrawal symptoms have been observed in some patients. The following events have been mentioned: insomnia, headache, nausea, anxiety, 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 post marketing reports of congestive heart failure in some patients receiving pregabalin. These reactions are mostly seen in elderly cardiovascular compromised patients during pregabalin treatment for a neuropathic indication. Pregabalin should be used with caution in these patients. Discontinuation of pregabalin may resolve the reaction.

Treatment of central neuropathic pain due to spinal cord injury

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

Suicidal ideation and behaviour

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

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

Reduced lower gastrointestinal tract function

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

Misuse, abuse potential or dependence

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

Encephalopathy

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

Nortriptyline

Suicide/suicidal thoughts or clinical worsening

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement

may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Withdrawal symptoms, including insomnia, irritability and excessive perspiration, may occur on abrupt cessation of therapy.

The use of nortriptyline in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms. If administered to overactive or agitated patients, increased anxiety and agitation may occur. In manic-depressive patients, nortriptyline may cause symptoms of the manic phase to emerge.

Cross sensitivity between nortriptyline and other tricyclic antidepressants is a possibility.

Patients with cardiovascular disease should be given nortriptyline only under close supervision because of the tendency of the drug to produce sinus tachycardia and to prolong the conduction time. Myocardial infarction, arrhythmia and strokes have occurred. Great care is necessary if nortriptyline is administered to hyperthyroid patients or to those receiving thyroid medication, since cardiac arrhythmias may develop.

The use of nortriptyline should be avoided, if possible, in patients with a history of epilepsy. If it is used, however, the patients should be observed carefully at the beginning of treatment, for nortriptyline is known to lower the convulsive threshold.

The elderly are particularly liable to experience adverse reactions, especially agitation, confusion and postural hypotension.

Troublesome hostility in a patient may be aroused by the use of nortriptyline.

Behavioural changes may occur in children receiving therapy for nocturnal enuresis.

If possible, the use of nortriptyline should be avoided in patients with narrow angle glaucoma or symptoms suggestive of prostatic hypertrophy.

The possibility of a suicide attempt by a depressed patient remains after the initiation of treatment. This possibility should be considered in relation to the quantity of drug dispensed at any one time.

When it is essential, nortriptyline may be administered with electroconvulsive therapy, although the hazards may be increased.

Both elevation and lowering of blood sugar levels have been reported. Significant hypoglycaemia was reported in a Type II diabetic patient maintained on chlorpropamide (250mg/day), after the addition of nortriptyline (125mg/day).

4.5 Drugs Interactions

Pregabalin

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

In vivo studies and population pharmacokinetic analysis

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

Oral contraceptives, norethisterone and/or ethinyl oestradiol

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

Central nervous system influencing medical products

Pregabalin may potentiate the effects of ethanol and lorazepam. In 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 post marketing 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.

Nortriptyline

Drug interactions: Under no circumstances should nortriptyline be given concurrently with, or within two weeks of cessation of, therapy with monoamine oxidase inhibitors. Hyperpyretic crises, severe convulsions and fatalities have occurred when similar tricyclic antidepressants were used in such combinations.

Nortriptyline should not be given with sympathomimetic agents such as adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine and phenylpropanolamine.

Nortriptyline may decrease the antihypertensive effect of guanethidine, debrisoquine, bethanidine and possibly clonidine. Concurrent administration of reserpine has been shown to produce a 'stimulating' effect in some depressed patients. It would be advisable to review all antihypertensive therapy during treatment with tricyclic antidepressants.

Barbiturates may increase the rate of metabolism of nortriptyline.

Anaesthetics given during tricyclic antidepressant therapy may increase the risk of arrhythmias and hypotension. If surgery is necessary, the drug should be discontinued, if possible, for several days prior to the procedure, or the anaesthetist should be informed if the patient is still receiving therapy.

Tricyclic antidepressants may potentiate the CNS depressant effect of alcohol.

The potentiating effect of excessive consumption of alcohol may lead to increased suicidal attempts or overdosage, especially in patients with histories of emotional disturbances or suicidal ideation.

Steady-state serum concentrations of the tricyclic antidepressants are reported to fluctuate significantly as cimetidine is either added to or deleted from the drug regimen. Higher than expected steady-state serum concentrations of the tricyclic antidepressant have been observed when therapy is initiated in patients already taking cimetidine. A decrease may occur when cimetidine therapy is discontinued.

Because nortriptyline's metabolism (like other tricyclic and SSRI antidepressants) involves the hepatic cytochrome P450IID6 iso-enzyme system, concomitant therapy with drugs also metabolised by this system may lead to drug interactions. Lower doses than are usually prescribed for either the tricyclic antidepressant or the other drug may therefore be required.

Greater than two-fold increases in previously stable plasma levels of nortriptyline have occurred when fluoxetine was administered concomitantly. Fluoxetine and its active metabolite, nor fluoxetine, have long half-lives (4-16 days for norfluoxetine).

Concomitant therapy with other drugs that are metabolised by this isoenzyme, including other antidepressants, phenothiazines, carbamazepine, propafenone, flecainide and encainide, or that inhibit this enzyme (eg, quinidine), should be approached with caution.

Supervision and adjustment of dosage may be required when nortriptyline is used with other anticholinergic drugs.

Nortriptyline plasma concentration can be increased by valproic acid. Clinical monitoring is therefore recommended.

4.6 Use in Special Populations (Such as Pregnant Women, Lactating Women, Paediatric Patients, Geriatric Patients Etc.)

Pregabalin

Women of childbearing potential/Contraception in males and females

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

Pregnancy

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

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

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

Breast-feeding

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

Fertility

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

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

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

Nortriptyline

Pregnancy

The safety of nortriptyline for use during pregnancy has not been established, nor is there evidence from animal studies that it is free from hazard; therefore the drug should not be administered to pregnant patients or women of childbearing age unless the potential benefits clearly outweigh any potential risk.

Breast-feeding

Nortriptyline is contra-indicated for the nursing mother and for children under the age of six years.

4.7. Effects on Ability to Drive and Use Machines

Pregabalin and Nortriptyline may have minor or moderate influence on the ability to drive and use machines. Pregabalin may cause dizziness and somnolence and therefore may influence the ability to drive or use machines. Patients are advised not to drive, operate complex machinery or engage in other potentially hazardous activities until it is known whether this medicinal product affects their ability to perform these activities. Nortriptyline may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating machinery or driving a car; therefore the patient should be warned accordingly.

4.8 Undesirable Effects

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

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

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

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

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

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

Pregabalin Adverse Drug Reactions

System Organ Class	**Adverse drug reactions**
Infections and infestations	
Common	Nasopharyngitis
Blood and lymphatic system disorders	
Uncommon	Neutropaenia
Not known	Bone-marrow depression, including agranulocytosis; aplastic anaemia; eosinophilia; purpura; Thrombocytopenia.
Immune system disorders	
Uncommon	*Hypersensitivity*

Rare	*Angioedema, allergic reaction*
Not known	*Rash, petechiae, urticaria, itching, photosensitisation* *(avoid excessive exposure to sunlight); oedema* *(General or of face and tongue), drug fever, crosssensitivity with other tricyclic drugs.*
Metabolism and nutrition disorders	
Common	Appetite increased
Uncommon	Anorexia, hypoglycaemia
Not known	Gynaecomastia in the male; syndrome of inappropriate secretion of antidiuretic hormone.
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
Not known	Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, drowsiness, agitation; insomnia, panic, nightmares; hypomania; exacerbation of psychosis; increased or decreased libido, impotence. Cases of suicidal ideation and suicidal behaviours have been reported during nortriptyline therapy or early treatment discontinuation
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
Not known	*Numbness, tingling, paraesthesia of extremities; in* *co-ordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, alteration of EEG patterns; tinnitus; dizziness; headache.* *Anticholinergic effects: Dry mouth and, rarely, associated sublingual adenitis or gingivitis; blurred vision, disturbance of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract.*
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
Not known	*Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke.*
Vascular disorders	
Uncommon	Hypotension, hypertension, hot flushes, flushing, peripheral coldness
Not known	Flushing
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
Not known	anorexia, epigastric distress, peculiar taste, stomatitis, abdominal cramps, black tongue, constipation, paralytic ileus parotid swelling
Hepatobiliary disorders	
Not known	Jaundice (simulating obstructive), altered liver function; hepatitis and liver necrosis

Very rare	Hepatic failure, hepatitis
Skin and subcutaneous tissue disorders	
Uncommon	Rash papular, urticaria, hyperhidrosis, *pruritus*
Rare	*Stevens Johnson syndrome,* cold sweat
Not known	*Alopecia*
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*
Not known	Nocturia; urinary frequency
Reproductive system and breast disorders	
Common	Erectile dysfunction
Uncommon	Sexual dysfunction, ejaculation delayed, dysmenorrhoea, breast pain
Not known	Amenorrhoea, breast discharge, breast enlargement, *gynaecomastia, testicular swelling;*
General disorders and administration site conditions	

Common	Oedema peripheral, oedema, gait abnormal, fall, feeling drunk, feeling abnormal,
Uncommon	Generalised oedema, *face oedema,* chest tightness, pain, pyrexia, thirst, chills,
Not known	Sweating; weakness, fatigue; alopecia.
Investigations	
Not known	Investigations Elevation or depression of blood sugar levels; weight gain or loss
Uncommon	Blood creatine phosphokinase increased, blood glucose increased, platelet count decreased, blood creatinine increased, blood potassium decreased, weight decreased
Rare	White blood cell count decreased

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

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

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

Paediatric population

The pregabalin safety profile observed in four paediatric studies in patients with partial seizures with or without secondary generalisation (12-week efficacy and safety study in patients 4 to 16 years of age, n=295; 14-day efficacy and safety study in patients 1 month to younger than 4 years of age, n=175; pharmacokinetic and tolerability study, n=65; and 1-year open label follow on safety study, n=54) was similar to that observed in the adult studies of patients with epilepsy. The most common adverse events observed in the 12-week study with pregabalin treatment were somnolence, pyrexia, upper respiratory tract infection, increased appetite, weight increased, and nasopharyngitis. The most common adverse events observed in the 14-day study with pregabalin treatment were somnolence, upper respiratory tract infection, and pyrexia.

Included in the following list are a few adverse reactions that have not been reported with this specific drug. However, the pharmacological similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when nortriptyline is administered.

Blood and lymphatic system disorders: Bone-marrow depression, including agranulocytosis; aplastic anaemia; eosinophilia; purpura; thrombocytopenia.

Immune system disorders: Petechiae, itching, photosensitisation (avoid excessive exposure to sunlight), drug fever, cross-sensitivity with other tricyclic drugs.

Endocrine disorders: Syndrome of inappropriate secretion of antidiuretic hormone.

Psychiatric disorders: Delusions, drowsiness, nightmares, hypomania, exacerbation of psychosis, impotence. Cases of suicidal ideation and suicidal behaviours have been reported during nortriptyline therapy or early treatment discontinuation.

Nervous system disorders: Numbness, tingling, tremors, extrapyramidal symptoms; seizures, alteration of EEG patterns, tinnitus.

Anticholinergic effects: Rarely associated sublingual adenitis or gingivitis, disturbance of accommodation, paralytic ileus, delayed micturition, dilation of the urinary tract.

Cardiac disorders: Palpitation, Myocardial infarction, arrhythmias, heart block, stroke.

Gastrointestinal disorders: Epigastric distress, peculiar taste, stomatitis, abdominal cramps, black tongue, paralytic ileus, parotid swelling.

Hepatobiliary disorders: Altered liver function, liver necrosis.

Skin and subcutaneous tissue disorders: Alopecia. Renal and urinary disorders: Nocturia.

Reproductive system disorders: Testicular swelling.

General disorders and administration site conditions: Sweating; weakness.

Withdrawal symptoms: Though these are not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache and malaise.

Class Effects: Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRs and TCAs. The mechanism leading to this risk is unknown

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.

Nortriptyline

***Signs and symptoms*:** 50mg of a tricyclic antidepressant can be an overdose in a child. Of patients who are alive at presentation, mortality of 0-15% has been reported. Symptoms may begin within several hours and may include blurred vision, confusion, restlessness, dizziness, hypothermia, hyperthermia, agitation, vomiting, hyperactive reflexes, dilated pupils, fever, rapid heart rate, decreased bowel sounds, dry mouth, inability to void, myoclonic jerks, seizures, respiratory depression, myoglobinuria renal failure, nystagmus, ataxia, dysarthria, choreoathetosis, coma, hypotension and cardiac arrhythmias. Cardiac conduction may be slowed, with prolongation of QRS complex and QT intervals, right bundle branch and AV block, ventricular tachyarrhythmia's (including Torsade de pointes and fibrillation) and death. Prolongation of QRS duration to more than 100msec is predictive of more severe toxicity. The absence of sinus tachycardia does not ensure a benign course. Hypotension may be caused by vasodilatation, central and peripheral alpha-adrenergic blockade and cardiac depression. In a healthy young person, prolonged resuscitation may be effective; one patient survived 5 hours of cardiac massage.

Treatment: Symptomatic and supportive therapy is recommended. Activated charcoal may be more effective than emesis or lavage to reduce absorption.

Ventricular arrhythmias, especially when accompanied by lengthened QRS intervals, may respond to alkalinisation by hyperventilation or administration of sodium bicarbonate. Serum electrolytes should be monitored and managed. Refractory arrhythmias may respond to propranolol, beryllium or lignocaine. Quinidine and procainamide usually should not be used because they may exacerbate arrhythmias and conduction already slowed by the overdose.

Seizures may respond to diazepam. Phenytoin may treat seizures and cardiac rhythm disturbances. Physostigmine may antagonise atrial tachycardia, gut immobility, myoclonic jerks and somnolence. The effects of physostigmine may be short-lived.

Diuresis and dialysis have little effect. Haemoperfusion is unproven. Monitoring should continue, at least until the QRS duration is normal.

5. Pharmacological Properties

5.1 Mechanism of Action

Pregabalin

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

Nortriptyline

Nortriptyline is a tricyclic antidepressant with actions and uses similar to these of Amitriplyline. It is the principle active metabolite of Amitriplyline.

5.2 Pharmacodynamic Properties

Pregabalin

Pharmacotherapeutic group: Anti-epileptics

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.

Paediatric population

The efficacy and safety of pregabalin as adjunctive treatment for epilepsy in paediatric patients below the age of 12 and adolescents has not been established. The adverse events observed in a pharmacokinetic and tolerability study that enrolled patients from 3 months to 16 years of age (n=65) with partial onset seizures 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.

Nortriptyline

Pharmacotherapeutic group: Antidepressants

In the treatment of depression Nortriptyline is given by mouth as the hydrochloride in doses equivalent to Nortriptyline 10 mg 3 or 4 times daily initially, gradually increased to 25 mg 4 times daily as necessary. A suggested initial dose for adolescents and the elderly is 10 mg thrice daily. Inappropriately high plasma concentrations of Nortriptyline have been associated with deterioration in antidepressant response. Since Nortriptyline has prolonged half-life, once daily dosage regimens are also suitable, usually given at night.

5.3 Pharmacokinetic Properties

Pregabalin

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

Absorption

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

Distribution

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

Biotransformation

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

Elimination

Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug.

Pregabalin mean elimination half-life is 6.3 hours. Pregabalin plasma clearance and renal clearance are directly proportional to creatinine clearance.

Dose adjustment in patients with reduced renal function or undergoing haemodialysis is necessary.

Linearity/non-linearity

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

Gender

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

Renal impairment

Pregabalin clearance is directly proportional to creatinine clearance. In addition, pregabalin is effectively removed from plasma by haemodialysis (following a 4 hour haemodialysis treatment plasma pregabalin concentrations are reduced by approximately 50%). Because renal

elimination is the major elimination pathway, dose reduction in patients with renal impairment and dose supplementation following haemodialysis is necessary.

Hepatic impairment

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

Paediatric population

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

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

Pregabalin 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 mg/kg basis.

Nortriptyline

Parts of metabolism of Nortriptyline include hydroxylation (possibly to active metabolites). Noxidation and conjugation with glucuronic acid. Nortriptyline is widely distributed throughout the body and is extensively bound to plasma and tissue protein. Plasma concentrations of Nortriptyline vary very widely between individuals and no simple correlation with therapeutic response has been established.

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 hyperactivity, 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.

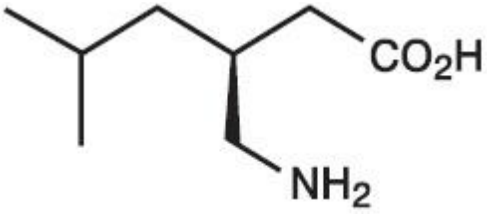
Nortriptyline

There are no preclinical data of relevance to the prescriber.

7. Description

Pregabalin

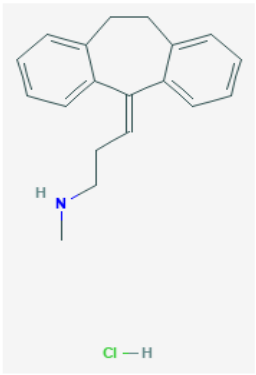
Pregabalin is described chemically as (S)-4-amino-3-(2-methylpropyl) butyric acid. The molecular formula is $C_8H_{17}NO_2$ and the molecular weight is 159.23. The chemical structure of pregabalin is:



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

Nortriptyline Hydrochloride

Nortriptyline Hydrochloride is 3-(10,11-dihydro-5H-dibenzo[a,d]cyclohept-5-ylidene)propyl(methyl)amine hydrochloride. The molecular formula is $C_{19}H_{21}N.HCl$ and the molecular weight is 299.8. The structural formula is as follows:



Nortriptyline Hydrochloride is white to off-white powder; odour slight and characteristic which is freely soluble in ethanol (95%) and in chloroform; sparingly soluble in water and in methanol; practically insoluble in ether, in benzene and in most other organic solvents.

Pregabalin and Nortriptyline Tablets are yellow coloured, round, biconvex, scored on one side, plain on other side & film coated tablets. The excipients used are Microcrystalline Cellulose, Sodium Starch Glycolate, Mannitol, Polyvinyl Pyrrolidone, Isopropyl Alcohol, Disodium Edetate, Starch, Magnesium Stearate, Colloidal Silicon Dioxide, Udomix-521, Opadry II 85F190000, Yellow Oxide of Iron and Titanium Dioxide

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

Not Available

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

PREGEB NT is available in 10 Tablets packed in Alu-Alu Blister.

8.4 Storage And Handing Instructions

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

9. PATIENT COUNSELLING INFORMATION

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 NT is and what it is used for

The active ingredient in PREGEB NT is Pregabalin and Nortriptyline Hydrochloride.

Pregabalin binds to an auxiliary subunit (α2-δ protein) of voltage-gated calcium channels in the central nervous system.

Nortriptyline is a tricyclic antidepressant with actions and uses similar to these of Amitriplyline. It is the principle active metabolite of Amitriplyline.

PREGEB NT tablets are indicated for treatment of diabetic neuropathy, post-herpetic neuralgia and fibromyalgia.

9.2 What you need to know before you take PREGEB NT

Do not take PREGEB NT:

- You are allergic (hypersensitive) to Pregabalin, Nortriptyline or any of the other ingredients of this medicine. An allergic reaction may include rash, itching, difficulty breathing or swelling of the face, lips, throat or tongue;
- If you have had a recent heart attack or heartbeat disorder;
- If you have severe liver disease;
- If you suffer from mania (abnormally raised mood);
- If you are breast-feeding;
- If the child is under 6 years of age;
- If you are taking, or have taken in the last two weeks, monoamine oxidase inhibitors (another type of antidepressant);
- If you are taking adrenaline-like drugs including ephedrine, isoprenaline, noradrenaline, phenylephrine and phenylpropanolamine. These drugs are often contained in cough and cold remedies.

Warnings and Precautions

Talk to your doctor or pharmacist before taking PREGEB NT.

- Some patients taking PREGEB NT 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 NT 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 NT 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 PREGEB NT 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 PREGEB NT 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 NT; 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 NT. If while taking PREGEB NT 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 NT have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.
- When PREGEB NT 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 NT or shortly after stopping PREGEB NT. If you experience a convulsion, contact your doctor immediately.
- There have been reports of reduction in brain function (encephalopathy) in some patients taking PREGEB NT when they have other conditions. Tell your doctor if you have a history of any serious medical conditions, including liver or kidney disease.
- If you feel suicidal or aggressive - tell your doctor.
- If you are agitated, overactive or suffer from schizophrenia;
- If you have a thyroid condition.
- If you have an enlarged prostate.
- If your child taking PREGEB NT has a change in behaviour.
- If you are going to have electroconvulsive therapy (electric shock).
- If you are diabetic.
- If you are going to receive an anaesthetic, e.g. for an operation – tell your doctor.
- If you have had an allergic reaction to another tricyclic antidepressant in the past.
- If you are pregnant, think you might be pregnant or planning to become pregnant or breast-feeding you should not take PREGEB NT unless your doctor tells you to.

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. These may be increased when first starting antidepressants, since these

medicines all take time to work, usually about two weeks but sometimes longer you may be more likely to think like this:

• If you have previously had thoughts about killing or harming yourself;

• If you are a young adult. Information from clinical trials has shown an increased risk of suicidal behaviour in adults aged less than 25 years with psychiatric conditions who were treated with an antidepressant.

If you have thoughts of harming or killing yourself at any time, **contact your doctor or go to 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. If any of the above applies to you, tell your doctor or pharmacist.

Children and adolescents

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

Other medicines and PREGEB NT

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

PREGEB NT and certain other medicines may influence each other (interaction). When taken with certain other medicines, PREGEB NT 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 PREGEB NT is taken together with medicines containing:

- Oxycodone – (used as a pain-killer)
- Lorazepam – (used for treating anxiety)
- Alcohol (you should not drink alcohol);
- Pregabalin may be taken with oral contraceptives.

Pregabalin with food, drink and alcohol

- PREGEB NT tablets may be taken with or without food.
- It is advised not to drink alcohol while taking Pregabalin.

Nortriptyline

The following medicines may interact with Nortriptyline

- guanethidine, debrisoquine, bethanidine, clonidine (used to treat high blood pressure);
- barbiturates (used for anxiety or to make you feel sleepy);
- alcohol (you should not drink alcohol);

- fluoxetine (another antidepressant);
- cimetidine (for heartburn and ulcers);
- phenothiazines (for mental illness);
- carbamazepine (for epilepsy);
- propafenone, flecainide, encainide, quinidine (for heartbeat disorders);
- valproic acid (medicine used for the treatment of epilepsy and bipolar disorder).

Pregnancy and breast-feeding

- Do not use PREGEB NT if you are pregnant or think you may be pregnant
- Do not use PREGEB NT if you are breast-feeding or planning to breast-feed
- If you are pregnant or breast feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Driving and using machines

PREGEB NT may have minor or moderate influence on the ability to drive and use machines Pregabalin may cause dizziness and somnolence and therefore may influence the ability to drive or use machines. Patients are advised not to drive, operate complex machinery or engage in other potentially hazardous activities until it is known whether this medicinal product affects their ability to perform these activities. Nortriptyline may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating machinery or driving a car; therefore the patient should be warned accordingly.

9. 3 How to take PREGEB NT

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

Taking this medicine

One tablet once daily or as directed by physician. Kindly follow physician's advice.

Adults

Dosage should begin at a low level and be increased as required. Alternatively, the total daily dose may be given once a day. Plasma levels of nortriptyline should be monitored and maintained in the optimum range of 50 to 150 ng/ml.

Elderly and Adolescents

Lower than usual dosages are recommended for elderly patients and adolescents. Lower dosages are also recommended for outpatients than for hospitalised patients who will be under close supervision. The physician should initiate dosage at a low level and increase it gradually, noting carefully the clinical response and any evidence of intolerance. Following remission, maintenance medication may be required for a longer period of time at the lowest dose that will maintain remission. If a patient develops minor side-effects, the dosage should be reduced. The

drug should be discontinued promptly if adverse effects of a serious nature or allergic manifestations occur.

If you take more PREGEB NT than you should

Go to the nearest casualty department or contact your doctor immediately. Take the tablet carton with you.

If you forget to take PREGEB NT

If you miss a dose, take one as soon as you can. If you have missed several doses, tell your doctor. Do not take a double dose to make up for a forgotten dose.

If you stop taking PREGEB NT

Do not stop taking the tablets or reduce the dose without telling your doctor first. If you suddenly stop taking the tablets you may feel sick (nausea), have a headache or feel generally unwell. 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, with seeing or hearing things (hallucinations), disorientation, decrease in sexual interest, irritability.
- Disturbance in attention, clumsiness, memory impairment, loss of memory, tremor, difficulty with speaking, tingling feeling, numbness, sedation, lethargy, fatigue, feeling abnormal.
- Blurred vision, double vision.
- Vertigo, problems with balance, fall.
- Dry mouth, constipation, vomiting, flatulence, diarrhoea, nausea, swollen abdomen.
- Difficulties with erection.
- Swelling of the body including extremities.
- Feeling drunk, abnormal style of walking.
- Weight gain.
- Muscle cramp, joint pain, back pain, pain in limb.
- Sore throat.

Uncommon: may affect up to 1 in 100 people

- Loss of appetite, weight loss, low blood sugar, high blood sugar.
- Change in perception of self, restlessness, depression, agitation, mood swings, difficulty finding words, hallucinations, abnormal dreams, panic attack, apathy, aggression, elevated mood, mental impairment, difficulty with thinking, increase in sexual interest, problems with sexual functioning including inability to achieve a sexual climax, delayed ejaculation.
- Changes in eyesight, unusual eye movement, changes in vision including tunnel vision, flashes of light, jerky movements, reduced reflexes, increased activity, dizziness on standing, sensitive skin, loss of taste, burning sensation, tremor on movement, decreased consciousness, loss of consciousness, fainting, increased sensitivity to noise, feeling unwell.
- Dry eyes, eye swelling, eye pain, weak eyes, watery eyes, eye irritation.
- Flushing, hot flushes.
- Difficulty breathing, dry nose, nasal congestion.
- Increased saliva production, heartburn, numb around mouth.
- Sweating, rash, chills, fever.
- Muscle twitching, joint swelling, muscle stiffness, pain including muscle pain, neck pain.
- Breast pain.
- Difficulty with or painful urination, incontinence.
- Weakness, thirst, chest tightness.
- Changes in blood and liver test results (blood creatinine phosphokinase increased, alanine amino transferase increased, aspartate aminotransferase increased, platelet count decreased, neutropaenia, increase in blood creatinine, decrease in blood potassium).
- Hypersensitivity, swollen face, itchiness, hives, runny nose, nose bleed, cough, snoring.
- Painful menstrual periods.
- Coldness of hands and feet.

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

- Abnormal sense of smell, swinging vision, altered perception of depth, visual brightness, vision loss.
- Dilated pupils, cross eyes.
- Cold sweat, tightness of the throat, swollen tongue.
- Inflammation of the pancreas.
- Difficulty in swallowing.
- Slow or reduced movement of the body.
- Difficulty with writing properly.
- Increased fluid in the abdomen.
- Fluid in the lungs.
- Convulsions.
- Changes in the recording of electrical changes (ECG) in the heart which correspond to heart rhythm disturbances.
- Muscle damage.
- Breast discharge, abnormal breast growth, breast growth in males.
- Interrupted menstrual periods.

- Kidney failure, reduced urine volume, urinary retention.
- Decrease in white blood cell count.
- Inappropriate behaviour.
- Allergic reactions (which may include difficulty breathing, inflammation of the eyes (keratitis) and a serious skin reaction characterized by rash, blisters, peeling skin and pain).
- Jaundice (yellowing of the skin and eyes).

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

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

(Not known: frequency cannot be estimated from the available data):

- Low or high blood pressure
- Fast or irregular heartbeat
- palpitations
- heart attack (myocardial infarction)
- stroke
- oedema (swelling of the ankles)
- confusion (especially in the elderly) with seeing or hearing things (hallucinations)
- not knowing where you are (disorientation)
- false beliefs (delusions)
- anxiety, restlessness, agitation
- not sleeping (insomnia)
- nightmares
- panic
- long-lasting abnormal mood
- worsening of mental illness
- numbness, tingling, pins and needles in the hands or feet
- coordination problems
- tremors
- abnormal movements
- fits (seizures)
- altered brainwave (EEG) patterns
- ringing in the ears (tinnitus)
- dry mouth
- rarely, inflamed glands under the tongue or inflammation of the gums (gingivitis) blurred vision, difficulty in focusing, dilated pupils
- constipation, blockage of the digestive tract unable to urinate or delayed urination
- rash
- itching
- light sensitivity
- swelling (oedema)

- fever
- reaction to other similar drugs
- blood disorders which may cause you to bruise easily, become anaemic or be unable to fight off infectionsfeeling sick (nausea) and vomiting not eating (anorexia)
- indigestion
- diarrhoea
- Constipation.
- peculiar taste
- inflamed mouth
- abdominal cramps
- black tongue
- development of breasts in men, breast enlargement and milk production in women
- increased or decreased sex drive
- failure to have an erection (impotence)
- swollen testicles
- altered blood sugar levels
- yellow eyes and skin (jaundice)
- altered liver function
- inflamed liver (hepatitis) and liver damage
- weight gain or loss
- sweating
- flushing
- urinating often and at night
- sleepiness
- dizziness
- weakness
- tiredness
- headache
- swollen glands
- Hair loss (alopecia).

An increased risk of bone fractures has been observed in patients taking this type of medicine..

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 PREGEB NT 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. 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 NT

- Keep out of the sight and reach of children.
- Do not use the tablets after the expiry date stated on the carton (EXP).
- Store protected from light & moisture, at a temperature not exceeding 30°C.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

9.6 Contents of the pack and other information

What PREGEB NT contains

The active substance is Pregabalin 75 mg and Nortriptyline 10 mg. The excipients used are Microcrystalline Cellulose, Sodium Starch Glycolate, Mannitol, Polyvinyl Pyrrolidone, Isopropyl Alcohol, Disodium Edetate, Starch, Magnesium Stearate, Colloidal Silicon Dioxide, Udomix-521, Opadry II 85F190000, Yellow Oxide of Iron and Titanium Dioxide.

What are the contents of the pack

PREGEB NT is available in 10 Tablets packed in Alu-Alu Blister.

10. Details of manufacturer

Manufactured by:

Akums Drugs & Pharmaceuticals Ltd.

At: Plot No. 26A, 27-30, Sector – 6A, IIE, SIDCUL,

Ranipur, Haridwar – 249403, Uttarakhand.

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Mfg Lic No. 4/UA/LL/2014 issued on 01.12.2017

12. DATE OF REVISION

Not Applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ PREGEB NT, 75, 10mg/DEC-20/01/PI