

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

PREGABA NT 50/10

1. Generic Name

Pregabalin and Nortriptyline Hydrochloride Tablets

2. Qualitative and quantitative composition

Each film coated tablet contains:

Pregabalin I.P.....50 mg

Nortriptyline Hydrochloride I.P.

Equivalent to Nortriptyline.....10 mg

Excipients.....q.s.

Colour: Titanium Dioxide I.P.

The Excipients used are Micro crystalline cellulose, Strach, Colloidal Silicon Dioxide, Polyvinyl Pyrrolidone, Sodium Lauryl Sulphate, Talcum, Crospovidone, Magnesium Stearate, Super coat white, Titanium Dioxide, Talcum.

3. Dosage form and strength

Dosage form: Film-coated tablet

Strength: Pregabalin 50 mg & Nortriptyline 10 mg

4. Clinical particulars

4.1 Therapeutic indication

It is indicated for the Treatment of neuropathic pain.

4.2 Posology and method of administration

Recommended oral dose of PREGABA NT 50/10 tablet is twice a day. It is advised to consult doctor for the dosage, as the frequency also depends on the patient's condition.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients of the tablet.
- Recent myocardial infarction, any degree of heart block or other cardiac arrhythmias.
- Severe liver disease.
- Mania.
- It is also 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 postmarketing experience of hypersensitivity reactions, including cases of angioedema. Pregabalin should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper airway swelling occur.

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

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

Vision-related effects

In 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 postmarketing reports of congestive heart failure in some patients receiving

pregabalin. These reactions are mostly seen in elderly cardiovascular compromised patients during pregabalin treatment for a neuropathic indication. Pregabalin should be used with caution in these patients. Discontinuation of pregabalin may resolve the reaction.

Treatment of central neuropathic pain due to spinal cord injury

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

Suicidal ideation and behaviour

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

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

Reduced lower gastrointestinal tract function

There are postmarketing reports of events related to reduced lower gastrointestinal tract function (e.g. intestinal obstruction, paralytic ileus, constipation) when pregabalin was 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 postmarketing experience, there are reports of respiratory failure and coma in patients taking pregabalin and other central nervous system (CNS) depressant medicinal products. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone.

Interactions and the elderly

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

Nortriptyline

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 overdose, 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 isoenzyme 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, norfluoxetine, 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 etc.)

Pregabalin

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

Pregabalin

The reported 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

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

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

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

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

Pregabalin

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	<p>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.</p> <p>Cases of suicidal ideation and suicidal behaviours have been reported during nortriptyline therapy or early treatment discontinuation</p>
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	<p>Numbness, tingling, paraesthesia of extremities; in co-ordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, alteration of EEG patterns; tinnitus; dizziness; headache.</p> <p>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.</p>
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 generalization (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.

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: https://www.torrentpharma.com/index.php/site/info/adverse_event_reporting By reporting side effects, you can help provide more information on the safety of this medicine

4.9 Overdose

Pregabalin

In the post marketing experience, the most commonly reported adverse reactions observed when pregabalin was taken in overdose included somnolence, confusional state, agitation, and restlessness. Seizures were also reported. In rare occasions, cases of coma have been reported.

Treatment of pregabalin overdose should include general supportive measures and may include haemodialysis if necessary.

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, myoglobinuric 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 tachyarrhythmias (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, bretylium 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 immotility, 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 ($\alpha 2\text{-}\delta$ 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 Amitriptyline. It is the principal active metabolite of Amitriptyline.

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) 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 $\geq 90\%$ 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 radio labelled 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 a 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 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.

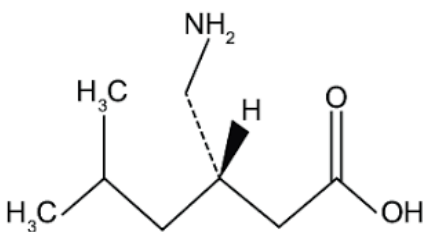
Nortriptyline

There are no preclinical data of relevance to the prescriber.

7. Description

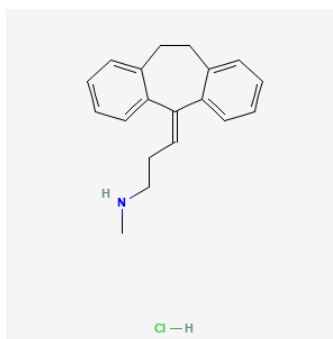
Pregabalin:

Pregabalin is (*S*)-4-amino-3-(2-methylpropyl) butyric acid. The empirical formula is $C_8H_{17}NO_2$ and its molecular weight is 159.2g/mol. The chemical structure of Pregabalin is:



Nortriptyline Hydrochloride:

Nortriptyline Hydrochloride is 3-(10,11-dihydro-5H-dibenzo [a,d]cyclohept-5-ylidene)propyl(methyl)amine hydrochloride. The empirical formula is $C_{19}H_{21}N_3HCl$ and its molecular weight is 299.8 g/mol. The chemical structure of Nortriptyline Hydrochloride is:



PREGABA NT 50/10

Pregabalin and Nortriptyline Hydrochloride Tablets are white to off- white coloured, round, biconvex, film coated tablets, scored on one side.

The Excipients used are Micro crystalline cellulose, Strach, Colloidal Silicon Dioxide, Polyvinyl Pyrrolidone, Sodium Lauryl Sulphate, Talcum, Crospovidone, Magnesium Stearate, Super coat white, Titanium Dioxide, Talcum.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable.

8.2 Shelf-life

Do not use later than date of expiry

8.3 Packaging information

PREGABA NT 50/10 is available in pack of 10 Tablets.

8.4 Storage and handing instructions

Store below 30°C. Protected from light & moisture.

Keep all the medicine out of reach of children.

9. Patient Counselling Information

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

- Have any allergies

- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10. Details of manufacturer

Synokem Pharmaceutical Ltd.
Plot No.: 56-57, Sector-6A,
I.I.E (SIDCUL), Ranipur (BHEL),
Haridwar-249403 (Uttarakhand)

11. Details of permission or licence number with date

Mfg Licence .No. 27/UA/2018 Issued on: 07.04.2022

12. Date of revision

MAY - 2024

MARKETED BY



TORRENT PHARMACEUTICALS LTD.

Torrent House, Off Ashram Road,
Ahmedabad-380 009, INDIA

IN/PREGABA NT 50/10 mg/May-2024/01/PI