

NEW ZEALAND DATA SHEET

NORPRESS



1. Product Name

Norpress, 10 mg & 25 mg, film coated tablet.

2. Qualitative and Quantitative Composition

Each film coated tablet contains 10 mg or 25 mg of nortriptyline (as hydrochloride).

Norpress tablets contain lactose.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

NORPRESS 10 mg tablets are yellow, film coated convex tablets, 5.6 mm diameter

NORPRESS 25 mg tablets are orange, film coated convex tablets, 8.7 mm diameter, with a scoreline on one side and blank on the other. The tablet can be divided into equal doses.

4. Clinical Particulars

4.1 *Therapeutic indications*

Nortriptyline hydrochloride is indicated for the relief of symptoms of depression. Endogenous depressions are more likely to be alleviated than are other depressive states.

Nortriptyline hydrochloride is indicated for the treatment of nicotine dependence as an aid to smoking cessation.

4.2 *Dose and method of administration*

For the relief of symptoms of depression

Nortriptyline hydrochloride is administered orally in the form of tablets. Lower than usual dosages are recommended for elderly patients. The use of lower dosages for outpatients is more important than for hospitalised patients who will be treated under close supervision. The physician should initiate dosage at a low level and increase it gradually, checking the clinical response carefully and noting any evidence of intolerance. Given the propensity of nortriptyline to induce SVT or ECG conduction defects, it is recommended physicians perform pre-treatment ECG's to establish a patient's cardiovascular health status. 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 medicine should be discontinued promptly if adverse effects of a serious nature or allergic manifestations occur.

Dose

Adult

25 mg 3 or 4 times daily; dosage should begin at a low level and be increased as required.

Doses above 100 mg per day are not recommended.

Special populations

Elderly

25 mg to 50 mg per day, in divided doses.

Adolescents

Not recommended for use in adolescent patients 13-18 years of age for the treatment of depression, unless under the supervision of a specialist.

As an aid in smoking cessation

Nortriptyline hydrochloride is administered orally in the form of tablets. Commence dosing prior to quit date at 25 mg/day and then increase to 75 – 100 mg when feasible over 10 days – 5 weeks. The recommended starting time is 10 – 28 days prior to the quit date and gradually increase to achieve a maintenance dose of 75 – 100 mg/day when possible for a total of up to 12 weeks. The physician should maintain therapeutic monitoring for vulnerable subjects, inadequate response and compliance concerns. If discontinuation is required nortriptyline should be tapered as withdrawal symptoms can occur with abrupt cessation.

Although 12 weeks is the usual treatment duration, the physician should have the discretion to use the medication for up to 6 months as a recent study shows some decrease in relapse to smoking with extended medication treatment.

Clinical experience with nortriptyline has not identified any differences in tolerability between the elderly and other adult patients. However, greater sensitivity of some elderly individuals cannot be ruled out. Elderly patients are more likely to have decreased renal function hence a reduced frequency of dosing maybe required.

Nortriptyline has not been tested in adolescents and since many adolescent smokers are not yet dependent on nicotine, nortriptyline for smokers under 18 years is not recommended.

4.3 Contraindications

- Nortriptyline is contraindicated for the treatment of depression in patients 12 years of age and under.
- Nortriptyline is contraindicated for the treatment of nocturnal enuresis.
- The concurrent use of nortriptyline hydrochloride or other tricyclic antidepressants with a monoamine oxidase inhibitor (MAOI) is contraindicated. Hyperpyretic crises, severe convulsions, and fatalities have occurred when similar tricyclic antidepressants were used in such combinations. It is advisable to discontinue the MAOI for at least 2 weeks before treatment with nortriptyline hydrochloride is started.
- Patients hypersensitive to nortriptyline hydrochloride should not be given the medicine. Cross-sensitivity between nortriptyline hydrochloride and other dibenzazepines is a possibility.
- Nortriptyline hydrochloride is contraindicated during the acute recovery period after myocardial infarction.

4.4 Special warnings and precautions for use

Clinical worsening and suicide risk

Patients of any age with Major Depressive Disorder may experience worsening of their depression and/or the emergence of suicidal ideation and behaviour (suicidality), whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Patients

should be closely monitored, especially at the beginning of therapy or when the dose is changed, until such improvement occurs.

There has been a long-standing concern that some antidepressants may have a role in the emergence of suicidality in some patients. The possible risk of increased suicidality in patients applies to all classes of antidepressant medicines, as available data are not adequate to exclude this risk for any antidepressant. Therefore, consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms. Generally, when stopping an antidepressant, doses should be tapered rather than stopped abruptly.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and paediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and non-psychiatric disorders, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric and non-psychiatric disorders.

Mania and bipolar disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with any antidepressant alone may increase the likelihood of a mixed/manic episode in patients at risk for bipolar disorder. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder. It should be noted that nortriptyline is not approved for use in treating bipolar depression.

Information for patients and families

Patients and their families should be alerted about the need to monitor for the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, mania, worsening of depression, and suicidal ideation, especially early during antidepressant treatment. Such symptoms should be reported to the patient's doctor, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

The patient has the right to treatment meeting appropriate ethical and professional standards, and the patient needs to be fully informed with frank discussion of risk/benefit issues relating to the medicines efficacy and safety when used in the treatment regimen proposed.

Patients with cardiovascular disease should be given nortriptyline hydrochloride only under close supervision because of the tendency of the medicine to produce sinus tachycardia and to prolong the conduction time. Myocardial infarction, arrhythmia, and strokes have occurred. The antihypertensive action of guanethidine and similar agents may be blocked. Because of its anticholinergic activity, nortriptyline hydrochloride should be used with great caution in patients who have glaucoma or a history of urinary retention. Patients with a history of seizures should be followed closely when nortriptyline hydrochloride is administered, because this medicine is known to lower the convulsive threshold.

In general, NORPRESS must not be used in patients with predisposing risk factors unless there is compelling clinical justification for which the potential medical benefit of smoking cessation

outweighs the potential risk of seizure. All patients should be assessed for predisposing risk factors which include;

- Concomitant administration of other medicinal products known to lower the seizure threshold (e.g. antipsychotics, antidepressants, tramadol, theophylline, systemic steroids, quinolones and sedating antihistamines)
- Excessive use of alcohol or sedatives
- History of head trauma
- Diabetes treated with hypoglycaemics or insulin
- Use of stimulants or anorectic products.

NORPRESS should be discontinued promptly if patients experience hypersensitivity reactions during treatment. Clinicians should be aware that symptoms may persist beyond the discontinuation of nortriptyline and clinical management should be provided accordingly.

Great care is required if nortriptyline hydrochloride is given to hyperthyroid patients or to those receiving thyroid medication, because cardiac arrhythmias may develop.

Alcohol

Excessive consumption of alcohol in combination with nortriptyline therapy may have a potentiating effect, which may lead to the danger of increased suicidal attempts or overdose especially in patients with histories of emotional disturbances or suicidal ideation. Therefore consumption of alcohol during NORPRESS treatment should be minimal or avoided.

Use in children

This medicine is not recommended for use in children, since safety and effectiveness in the paediatric age group have not been established.

Cardiovascular disorders

Nortriptyline should be used with caution in patients with cardiovascular disease, including heart failure, conduction disorders (eg AV block grades I to III), or arrhythmias. Cardiovascular and ECG monitoring should be undertaken in such patients. An ECG should be performed prior to starting treatment, at steady state, after an increase in dose or after starting any potentially interacting medicine.

Tricyclic Antidepressant medicines, including nortriptyline, particularly when given in high doses, have been reported to produce QTc prolongation, arrhythmias (including Torsades de Pointes (TdP), sinus tachycardia, and prolongation of the conduction time. Myocardial Infarction and stroke have also been reported with medicines of this class (see section 4.8).

Nortriptyline should be used with caution in patients with risk factors for QTc prolongation/TdP including congenital long QT syndrome, age >65 years, female sex, structural heart disease/LV dysfunction, medical conditions such as renal or hepatic disease, use of medicines that inhibit the metabolism of nortriptyline, and the concomitant use of other QTc prolonging medicines (see section 4.5). Hypokalaemia and hypomagnesaemia should be corrected prior to treatment.

Consideration should be given to stopping nortriptyline treatment or reducing the dose if the QTc interval is >500 ms or increases by >60 ms.

General

If the medicine is given to overactive or agitated patients, increased anxiety and agitation may occur. Troublesome patient hostility may be aroused by the use of nortriptyline hydrochloride. As may happen with other medicines of its class, epileptiform seizures may accompany its administration. When it is essential, the medicine may be administered concurrently with electroconvulsive therapy, although the hazards may be increased.

Discontinue the medicine for several days, if possible, prior to elective surgery.

Both elevation and lowering of blood sugar levels have been reported. A case of significant hypoglycaemia has been reported after the addition of nortriptyline (125 mg/day) in a type II diabetic patient maintained on chlorpropamide (250 mg/day).

Prior to initiation of combination therapy with a Nicotine Transdermal System (NTS) prescribers should consult the prescribing information of the relevant NTS. If combination therapy is used, monitoring for treatment-emergent elevations of blood pressure is recommended. Likewise an ECG prior to initiating therapy is recommended.

4.5 Interaction with other medicines and other forms of interaction

Cimetidine

Steady-state serum concentrations of the tricyclic antidepressants are reported to fluctuate significantly when cimetidine is either added or deleted from the medicine regimen. Serious anticholinergic symptoms (severe dry mouth, urinary retention, blurred vision) have been associated with elevations in the serum levels of tricyclic antidepressants when cimetidine is added to the medicine regimen. In addition, higher than expected steady-state serum concentrations of tricyclic antidepressants have been observed when therapy is initiated in patients already taking cimetidine.

In well-controlled patients undergoing concurrent therapy with cimetidine, a decrease in the steady-state serum concentrations of the tricyclic antidepressants may occur when cimetidine therapy is discontinued. The therapeutic efficacy of the tricyclic antidepressant may be compromised in these patients as the cimetidine is discontinued. Several of the tricyclic antidepressants have been cited in these reports. There have been greater than two-fold increases in previously stable plasma levels of other antidepressants, including nortriptyline, when fluoxetine hydrochloride has been administered in combination with these agents. Fluoxetine and its active metabolite, norfluoxetine, have long half-lives (4 to 16 days for norfluoxetine) that may affect strategies during conversion from one medicine to the other.

Reserpine

Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients.

Anticholinergic / sympathomimetic medicines

Close supervision and careful adjustment of the dosage are required when nortriptyline hydrochloride is used with other anticholinergic medicines and sympathomimetic medicines.

Alcohol

The patient should be informed that the response to alcohol may be exaggerated.

Quinidine

The concomitant administration of quinidine and nortriptyline may result in a significantly longer plasma half-life, higher AUC and lower clearance of nortriptyline.

Guanethidine and similar agents, thyroid medication, alcohol (see section 4.4).

Medicines metabolised by P450IID6

A subset (3% to 10%) of the population has reduced activity of certain medicine metabolising enzymes such as the cytochrome P450 isoenzyme P450IID6. Such individuals are referred to as "poor metabolisers" of medicines such as debrisoquin, dextromethorphan, and the tricyclic antidepressants. These individuals may have higher than expected plasma concentrations of tricyclic antidepressants when given usual doses. In addition, certain medicines that are metabolised by this isoenzyme, including many antidepressants (tricyclic antidepressants, selective serotonin reuptake inhibitors, and others), may inhibit the activity of this isoenzyme, and thus may make normal

metabolisers resemble poor metabolisers with regard to concomitant therapy with other medicines metabolised by this enzyme system, leading to medicine interactions.

Concomitant use of tricyclic antidepressants with other medicines metabolised by cytochrome P450IID6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other medicine. Therefore, co-administration of tricyclic antidepressants with other medicines that are metabolised by this isoenzyme, including other antidepressants, phenothiazines, carbamazepine, and Type 1C antiarrhythmics (e.g., propafenone, flecainide, and encainide), or that inhibit this enzyme (e.g., quinidine), should be approached with caution.

Medicines that can prolong the QT interval

The risk of QTc prolongation and/or ventricular arrhythmias (e.g. Torsades de Pointes) is increased with concomitant use of other medicines which prolong the QTc interval (e.g. some antipsychotics and antibiotics). Please check the data sheet of other medicines administered for information on their effects on the QTc interval.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category C

Nortriptyline should only be used in pregnancy if considered necessary, taking into account the risks of untreated depression, and under the close supervision of a physician.

Epidemiological studies have suggested an increased risk of congenital abnormalities associated with use of tricyclic antidepressants in pregnancy. There is evidence of interference with central monoamine neurotransmission in rats.

Neonates should be observed if maternal use of nortriptyline has continued into the later stages of pregnancy, particularly into the third trimester.

Neonates exposed to tricyclic antidepressants, late in the third trimester have showed drug withdrawal symptoms such as dyspnoea, lethargy, colic irritability, hypotension or hypertension and tremor or spasms.

Epidemiological data suggests that the use of tricyclic antidepressants in pregnancy may be associated with an increase in pre-term delivery.

Breast-feeding

Safe use of nortriptyline during lactation has not been established; therefore, when the medicine is administered to nursing mothers the potential benefits must be weighed against the possible hazards.

Fertility

No data available. For pre-clinical fertility data refer to section 5.3.

4.7 Effects on ability to drive and use machines

Nortriptyline hydrochloride 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

Note: Included in the following list are a few adverse reactions that have not been reported with this specific medicine. However, the pharmacologic similarities among the tricyclic antidepressant medicines require that each of these reactions be considered when nortriptyline is administered.

Class effects

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

Cardiovascular

Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias (including ventricular tachycardia, ventricular fibrillation and Torsades de Pointes), stroke, ECG changes (including QTc prolongation, non-specific ST and T wave changes, and AV conduction disorders such as heart block, bundle branch block and widened QRS complex).

Psychiatric

Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia, panic, nightmares; hypomania; exacerbation of psychosis.

Neurologic

Numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, alteration of EEG patterns; tinnitus.

Anticholinergic

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.

Allergic

Skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); oedema (general or of face and tongue), medicine fever, cross-sensitivity with other tricyclic medicines.

Haematologic

Bone-marrow depression, including agranulocytosis; aplastic anaemia; eosinophilia; purpura; thrombocytopenia.

Gastrointestinal

Nausea and vomiting, anorexia, epigastric distress, diarrhoea; peculiar taste, stomatitis, abdominal cramps, black tongue, constipation, paralytic ileus.

Endocrine

Gynecomastia in the male; breast enlargement and galactorrhoea in the female; increased or decreased libido, impotence; testicular swelling; elevation or depression of blood sugar level; syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Other

Jaundice (simulating obstructive); altered liver function, hepatitis, and liver necrosis; weight gain or loss; perspiration; flushing; urinary frequency, nocturia; drowsiness; dizziness, weakness, fatigue; headache; parotid swelling; alopecia.

Withdrawal symptoms

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

Deaths may occur from overdosage with this class of medicines. Multiple medicine ingestion (including alcohol) is common in deliberate tricyclic antidepressant overdose. As the management is complex and changing, it is recommended that the physician contact a Poison Control Centre for current information on treatment. Signs and symptoms of toxicity develop rapidly after tricyclic antidepressant overdose; therefore, hospital monitoring is required as soon as possible.

Manifestations

Critical manifestations of overdose include: cardiac dysrhythmias (tachycardia, arrhythmias (including Torsades de Pointes), QTc prolongation, conduction disorders, shock, heart failure; in very rare cases cardiac arrest, severe hypotension, convulsions, and CNS depression, including coma. Changes in the electrocardiogram, particularly in QRS axis or width, are clinically significant indicators of tricyclic antidepressant toxicity. Other signs of overdose may include: confusion, disturbed concentration, transient visual hallucinations, dilated pupils, agitation, hyperactive reflexes, stupor, drowsiness, muscle rigidity, vomiting, hypothermia, hyperpyrexia, or many of the symptoms listed under section 4.8.

Management

General

Obtain an ECG and immediately initiate cardiac monitoring. Protect the patient's airway, establish an intravenous line and initiate gastric decontamination. A minimum of six hours of observation with cardiac monitoring and observation for signs of CNS or respiratory depression, hypotension, cardiac dysrhythmias and/or conduction blocks, and seizures is necessary. If signs of toxicity occur at any time during this period, extended monitoring is required. There are case reports of patients succumbing to fatal dysrhythmias late after overdose; these patients had clinical evidence of significant poisoning prior to death and most received inadequate gastrointestinal decontamination. Monitoring of plasma medicine levels should not guide management of the patient.

Gastrointestinal decontamination

All patients suspected of tricyclic antidepressant overdose should receive gastrointestinal decontamination. This should include large volume gastric lavage followed by activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage. Emesis is contraindicated.

Cardiovascular

A maximal limb-lead QRS duration of ≥ 0.10 seconds may be the best indication of the severity of the overdose. Intravenous sodium bicarbonate should be used to maintain the serum pH in the range of 7.35 to 7.45. If the pH response is inadequate, hyperventilation may also be used. Concomitant use of hyperventilation and sodium bicarbonate should be done with extreme caution, with frequent pH monitoring. A pH > 7.60 or a $pCO_2 < 20$ mm Hg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium or phenytoin. Type 1A and 1C antiarrhythmics are generally contraindicated (e.g., quinidine, disopyramide, and procainamide). In rare instances, haemoperfusion may be beneficial in acute refractory cardiovascular instability in patients with acute toxicity. However, haemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis generally have been reported as ineffective in tricyclic antidepressant poisoning.

CNS

In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration. Seizures should be controlled with benzodiazepines, or if these are ineffective, other

anticonvulsants (e.g., phenobarbital, phenytoin). Physostigmine is not recommended except to treat life-threatening symptoms that have been unresponsive to other therapies, and then only in consultation with a poison control centre.

Psychiatric follow-up

Since overdose is often deliberate, patients may attempt suicide by other means during the recovery phase. Psychiatric referral may be appropriate.

Paediatric management

The principles of management of child and adult overdoses are similar. It is strongly recommended that the physician contact the local poison control centre for specific paediatric treatment.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidepressant, ATC code: N06AA10

Mechanism of action

Nortriptyline hydrochloride is a tricyclic antidepressant. The mechanism of mood elevation by such tricyclic antidepressants is at present unknown. Nortriptyline hydrochloride is not a monoamine oxidase inhibitor (MAOI). It inhibits the activity of such diverse agents as histamine, 5-hydroxytryptamine and acetylcholine. It increases the pressor response of noradrenaline but blocks the pressor response of phenethylamine. Studies suggest that nortriptyline hydrochloride interferes with the transport, release, and storage of catecholamines. Operant conditioning techniques in rats and pigeons suggest that nortriptyline hydrochloride has a combination of stimulant and depressant properties.

5.2 Pharmacokinetic properties

Optimal responses to nortriptyline have been associated with plasma concentrations of 50 to 150 mcg/L. Higher concentrations may be associated with more adverse experiences. Plasma concentrations are difficult to measure, and physicians should consult with the laboratory professional staff. Older patients have been reported to have larger plasma concentrations of the active nortriptyline metabolite, 10-hydroxy-nortriptyline. In one case, this was associated with apparent cardiotoxicity despite nortriptyline concentrations within the "therapeutic range". Clinical findings should predominate over plasma concentrations as primary determinants of dosage changes.

5.3 Preclinical safety data

Animal reproduction studies have yielded inconclusive results. Daily feeding of nortriptyline at a diet level of 0.05 percent from Day 5 to Day 20 of the gestation period had no deleterious effects on foetal development of rabbits. Rats fed diets containing the equivalent of 30 mg per kg daily from the time of weaning until maturity and during breeding studies showed no indications of teratogenesis in the foetuses of two litters.

6. Pharmaceutical Particulars

6.1 List of excipients

Norpress tablets also contain lactose, maize starch, magnesium stearate, polyvinyl alcohol, talc, titanium dioxide, macrogel/PEG 3350 and lecithin. In addition, the 10 mg tablets also contain

quinoline yellow and iron oxide yellow. The 25 mg tablets also contain sunset yellow FCF, brilliant blue FCF and allura red AC.

Norpress tablets are gluten free.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

NORPRESS 10 mg tablets: PVC/PVDC/AL blister packs of 50 and 100 tablets.

NORPRESS 25 mg tablets: PVC/PVDC/AL blister packs of 50, 100, 180, 250, and 500 tablets.

Not all pack types and sizes may be marketed

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Mylan New Zealand Ltd
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Ellerslie
AUCKLAND
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9. Date of First Approval

5 December 1985

10. Date of Revision of the Text

18 April 2018 Revised to SmPC format
