

**NEW ZEALAND DATA SHEET****Nortriptyline NRIM*****Nortriptyline (as hydrochloride) 10 mg and 25 mg Tablets***

This product may not be interchangeable with similar products on the New Zealand market

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**Presentations**

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Nortriptyline NRIM 10 mg tablets are white to off-white round biconvex tablets, debossed 'NM' on one side and '10' on the other side.

Nortriptyline NRIM 25 mg tablets are white to off-white round biconvex tablets, debossed 'NM' on one side and '25' on the other side.

Do not halve tablet. Dose equivalence when the tablet is divided has not been established.

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**Indications**

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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.

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**Dosage and Administration**

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***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.

**Usual adult dose**

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.

**Elderly patients**

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

**Adolescent depression**

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.

Do not halve tablet. Dose equivalence when the tablet is divided has not been established

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## Contraindications

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- 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.

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## Warnings and Precautions

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### 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. 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.

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.

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.

## Information for patients and families

Patients and their caregivers should be alerted to 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 medicine's 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. Arrhythmias and hypotension can occur in patients without prior risk, especially when high doses are prescribed, therefore patients should be monitored accordingly.

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, Nortriptyline NRIM 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.

Nortriptyline NRIM should be discontinued promptly if patients experience hypersensitivity reactions during treatment. Cross sensitivity between nortriptyline and other tricyclic antidepressants is a possibility. Clinicians should be aware that symptoms may persist beyond the discontinuation of nortriptyline and clinical management should be provided accordingly.

Caution should be exercised when treating patients with advanced liver disease.

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

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

If possible, the use of nortriptyline should be avoided in patients with narrow angle glaucoma, raised intra-ocular pressure or symptoms suggestive of urinary retention or prostatic hypertrophy.

In patients developing throat pain, fever and flu symptoms during the first 10 weeks of treatment, it is recommended that a full blood count is conducted to exclude agranulocytosis.

Hyperpyrexia has been reported during treatment with tricyclic antidepressants together with anticholinergic or with neuroleptics, especially during hot weather.

The tablets contain lactose monohydrate. Patients with rare hereditary diseases such as galactose intolerance, Lapp lactose deficiency, or glucose-galactose malabsorption should not use this medication.

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 Nortriptyline NRIM treatment should be minimal or avoided.

### **Cardiovascular disorders**

Nortriptyline should be used with caution in patients with cardiovascular disease, including heart failure, conduction disorders (e.g. 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 Adverse Effects).

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 Interactions).

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 >500ms or increases by >60ms.

### **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.

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.

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). Adjustment of anti-diabetic therapy may, therefore, be necessary.

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.

### ***Use in 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 shown 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.

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 fetuses of two litters.

### ***Use in lactation***

Nortriptyline is excreted in limited amounts. The relative infant dose is low and serum levels have been reported as low or undetectable. 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.

### ***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.

### ***Use in children***

Nortriptyline should not be used in the treatment of depression in children and adolescents under the age of 18 years. Studies in depression of this age group did not show a beneficial effect for class of tricyclic antidepressants. Studies with other classes of antidepressants (SSRIs and SNRIs) have shown risk of suicidality, self-harm and hostility to be related to these compounds. This risk cannot be excluded with nortriptyline. In addition, nortriptyline is associated with a risk of cardiovascular adverse events in all age groups. Furthermore, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are not available.

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## **Adverse Effects**

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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), 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), peripheral oedema, stroke.

### **Psychiatric**

Confusional states (especially in the elderly) with hallucinations, disorientation, delusions, anxiety, restlessness, agitation, insomnia, panic, hypomania, mania, exacerbation of psychosis, changes in sleep patterns (including nightmares), irritability and decreased libido.

### **Neurologic**

Dizziness, headache, concentration disorders, clumsiness, taste disorders, numbness, tingling, paraesthesias 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), fever, cross-sensitivity with other tricyclic medicines.

**Haematologic**

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

**Gastrointestinal**

Constipation, diarrhoea, nausea and vomiting, tongue oedema, increased salivary glands, loss of appetite, anorexia, epigastric distress, peculiar taste, stomatitis, abdominal cramps, black tongue, 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, cholestasis, hepatitis, and liver necrosis, weight gain or loss, perspiration, flushing, sweating, urinary frequency, nocturia, drowsiness, weakness, fatigue, parotid swelling, alopecia, mouth or gum problems, erection disorders.

**Withdrawal symptoms**

Insomnia, irritability, nausea, headache and excessive perspiration, may occur on abrupt cessation of therapy. Unknown Cases of suicidal ideation and suicidal behaviours have been reported during therapy or early treatment discontinuation.

**Examinations**

Weight increase, increased intraocular pressure, weight loss, abnormal liver function, increased blood alkaline phosphatase, increased transaminase, and changes in blood sugar levels.

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**Interactions**

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**MAO Inhibitors**

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.



## Alcohol

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 a history of emotional disturbances or suicidal ideation.

## Anaesthetics

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.

## 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 such as adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine and phenylpropanolamine.

Supervision and adjustment of dosage may be required when nortriptyline is used with other anticholinergic drugs due to an increased risk of ileus, delirium and hyperpyrexia.

## Antifungals

Antifungal medication such as fluconazole and terbinafine increase the serum concentration of tricyclic antidepressants and the associated toxicity. Syncope and Torsades de Pointes have been reported.

## Antihypertensive therapy

Nortriptyline may decrease the antihypertensive effect of guanethidine, debrisoquine, bethanidine, methyldopa and possibly clonidine. It would be advisable to review all antihypertensive therapy during treatment with tricyclic antidepressants.

## Reserpine

Concurrent administration of reserpine has been shown to produce a 'stimulating' effect in some depressed patients.

## 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.

## 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 debrisoquine, 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.

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.

## Medicines that affect the QT interval

The combination of nortriptyline with medications that increase the QT interval such as quinidine, antihistamines (such as astemizole and terfenadine), some antipsychotics (mainly pimozide and sertindole), cisapride, halofrantine, and sotalol can increase the risk for QT prolongation and/or ventricular arrhythmias (e.g. Torsades de Pointes). TCAs have some characteristics of class I antiarrhythmics. Caution is warranted in combination with antiarrhythmics from this class, with beta-receptor blockers and with calcium antagonists (especially verapamil) due to a potentiating effect on the AV-conduction time and negative inotropic effects. In combination with class I antiarrhythmics and loop and thiazide diuretics attention should be paid to potential inhibitory effect on the QT time due to potassium loss. Please check the data sheet of other medicines administered for information on their effects on the QT interval.

## Quinidine

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

## Others

**Guanethidine and similar agents, thyroid medication, alcohol** - see Warnings and Precautions.

**Barbiturates** may increase the rate of metabolism of nortriptyline.

In combination with **levothyroxine** antidepressants can give rise to hyperthyroidism and levothyroxine may strengthen the antidepressant effect

The metabolism of **levodopa** in the intestine may be accelerated, possibly through delay of peristalsis.

TCA's may increase the risk of seizure in patients using **tramadol**.

“Serotonin syndrome” (changes in cognition, behaviour, function of the autonomic nervous system and neuromuscular activity) has been reported when nortriptyline is administered together with **serotonin enhancing medications**.

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## Overdose

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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 the National Poisons Centre (ph. 0800 POISON or 0800 764 766) 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 Adverse Effects.

### 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  $\geq 0.10$  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  $p\text{CO}_2 < 20$  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 overdosage 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 overdosages are similar. It is strongly recommended that the physician contact the local poison control centre for specific paediatric treatment.

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## Further Information

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**Actions**

Nortriptyline hydrochloride is a tricyclic antidepressant with actions and uses similar to those of amitriptyline. It is the principal active metabolite of amitriptyline.

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 is less anticholinergic than amitriptyline, whilst having stronger antihistaminic effects. 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.

Nortriptyline has prolonged half-life hence once daily dosage regimens are suitable, usually given at night.

## **Pharmacokinetics**

### **Absorption**

Oral administration results in maximum plasma concentrations in approximately 5 hours ( $T_{max} = 5.5 \pm 1.9$  hours; range 4.0-8.8 hours). The mean oral bioavailability is 51% ( $F_{abs} = 0.51 \pm 0.05$ ; range 0.46-0.59).

### **Distribution**

The apparent volume of distribution ( $V_d$ ), estimated after intravenous administration is  $1633 \pm 268$  L; range 1460 to 2030 ( $21 \pm 4$  L/kg). Plasma protein binding is approximately 93%. Nortriptyline crosses the placental barrier.

### **Metabolism**

The metabolism of nortriptyline is by demethylation and hydroxylation followed by conjugation with glucuronic acid. The metabolism is subject to genetic polymorphism (CYP2D6). The main active metabolite is 10-hydroxynortriptyline, which exists in a cis and a trans form, the trans form is dominant. N demethylnortriptyline is also formed to some extent. The metabolites have the same profile as nortriptyline but are weaker. Trans 10-hydroxynortriptyline is more potent than the cis form. 10-hydroxynortriptyline dominates in the plasma but most of the metabolites are conjugated.

### **Elimination**

The elimination half-life ( $t_{1/2}$ ) after oral nortriptyline administration is approximately 26 hours ( $25.5 \pm 7.9$  hours; range 16-38 hours). The mean systemic clearance (Cl) is  $30.6 \pm 6.9$  L/h; ranging from 18.6 to 39.6 L/hour. Excretion is mainly via the urine. The renal elimination of unchanged nortriptyline is insignificant (about 2%). In lactating mothers nortriptyline is excreted in small quantities into breast milk. The concentration ratio of milk/plasma concentration in women is 1:2. The estimated daily infant exposure is on average equivalent to 2% of the maternal weight-related dose of nortriptyline (mg/kg). Steady state plasma levels of nortriptyline for most patients are reached within one week.

In elderly patients, longer half-lives and reduced oral clearance (CLO) values due to reduced metabolic rate have been shown.

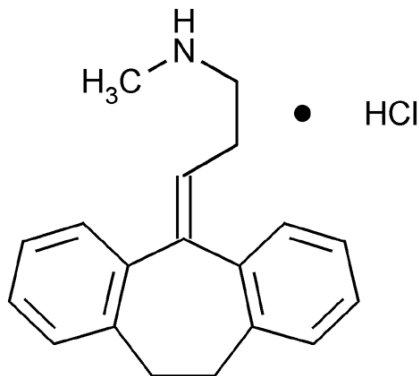
Moderate to severe liver disease may reduce hepatic clearance resulting in higher plasma levels.

Renal failure has no significant effect on nortriptyline kinetics.

### **Plasma levels**

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.

**Other**



Nortriptyline hydrochloride is 1-Propanamine, 3-(10,11-dihydro-5H-dibenzo[a,d] cyclohepten-5-ylidene)-N-methyl-hydrochloride.

Its molecular weight is 299.8, and its empirical formula is C<sub>19</sub>H<sub>21</sub>N.HCl.

**Excipients**

Lactose monohydrate

Starch – maize

Magnesium stearate

## Pharmaceutical Precautions

***Shelf life***

2 years

***Special precautions for storage***

Store below 25°C. Store in the original container.

## Medicine Schedule

Prescription Medicine

## Package Quantities

Blister packs of 100 tablets

## Sponsor Details

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BNM Group  
39 Anzac Road  
Browns Bay  
Auckland 0753

Ph: 0800 565 633

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## Date of Preparation

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09 May 2013