# NORTRIPTYLINE 10MG TABLETS
# NORTRIPTYLINE 25MG TABLETS

**UKPAR**

## TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lay Summary</td>
<td>2</td>
</tr>
<tr>
<td>Scientific discussion</td>
<td>3</td>
</tr>
<tr>
<td>Steps taken for assessment</td>
<td>12</td>
</tr>
<tr>
<td>Steps taken after authorisation – summary</td>
<td>13</td>
</tr>
<tr>
<td>Summary of Product Characteristics</td>
<td></td>
</tr>
<tr>
<td>Product Information Leaflet</td>
<td></td>
</tr>
<tr>
<td>Labelling</td>
<td></td>
</tr>
</tbody>
</table>
NORTRIPTYLINE 10MG TABLETS
NORTRIPTYLINE 25MG TABLETS

LAY SUMMARY

On 1\textsuperscript{st} May 2009, the MHRA granted NRIM Limited Marketing Authorisations (licences) for the medicinal products Nortriptyline 10 and 25mg Tablets (PL 20620/0018-9). These are prescription only medicines (POM) to relieve the symptoms of depression and to help stop children bed-wetting.

Nortriptyline 10 and 25mg Tablets contain the active ingredient nortriptyline hydrochloride, a tricyclic antidepressant.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Nortriptyline 10 and 25mg Tablets outweigh the risks, hence Marketing Authorisations have been granted.
NORTRIPTYLINE 10MG TABLETS
NORTRIPTYLINE 25MG TABLETS

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>4</td>
</tr>
<tr>
<td>Pharmaceutical assessment</td>
<td>5</td>
</tr>
<tr>
<td>Preclinical assessment</td>
<td>7</td>
</tr>
<tr>
<td>Clinical assessment (including statistical assessment)</td>
<td>8</td>
</tr>
<tr>
<td>Overall conclusions and risk benefit assessment</td>
<td>11</td>
</tr>
</tbody>
</table>
**INTRODUCTION**

Based on the review of the data on quality, safety and efficacy, the UK granted Marketing Authorisations for the medicinal products Nortriptyline 10 and 25mg Tablets to NRIM Limited (PL 20620/0018-9) on 1st May 2009. The products are prescription-only medicines.

These are national abridged applications for Nortriptyline 10 and 25mg Tablets claiming essential similarity to the originator product, Allegron 10 and 25mg Tablets, first licensed to Eli Lilly and Company Limited on 14th February 1983. Following a change of ownership, the marketing authorisation holder for Allegron 10 and 25mg Tablets is now King Pharmaceuticals Limited.

The products contain the active ingredient nortriptyline hydrochloride and are indicated for the relief of symptoms of depression. It may also be used for the treatment of some cases of nocturnal enuresis.

Nortriptyline is a tricyclic antidepressant with actions and uses similar to those of amitriptyline. It is the principal active metabolite of amitriptyline. Its action is believed to be related to its ability to block the reuptake of norepinephrine, which prolongs the action of this neurotransmitter. The exact mechanism of action is not known.
Active Substance

INN: Nortriptyline HCl

Chemical Name: i) 3-(10,11-dihydro-5H-dibenzo[a,d][7]annulen-5-ylidene)-N-methylpropan-1-amine hydrochloride
ii) 5- (a- methylaminopropylidene)dibenz[a,d] cyclohepta-[1,4] diene hydrochloride.
iii) 3-(10,11- dihydro -5H-dibeno[a,d] cyclohepten-5-ylidene)-N-methyl propylamine hydrochloride.
iv) 10, 11- dihydro-5-( 3- methylaminopropylidene)-5Hdibenzo[a,d]-{1,4}cycloheptene hydrochloride.

Molecular Formula: C_{19}H_{21}N.HCl

Chemical Structure:

![Chemical Structure Image]

Molecular Weight: 299.8

Appearance: A white or almost white crystalline powder, sparingly soluble in water, soluble in ethanol (96%) and in methylene chloride.

Chirality: The drug substance is achiral

Polymorphism: No polymorphism has been observed.

Nortriptyline hydrochloride is the subject of a European Pharmacopoeia monograph.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance nortriptyline hydrochloride. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting the proposed retest period when stored in the approved containers.
Other Ingredients
Other ingredients consist of pharmaceutical excipients lactose monohydrate, maize starch and magnesium stearate. All excipients comply with their respective European Pharmacopoeia monograph. Satisfactory certificates of analysis have been provided for all excipients.

Lactose monohydrate is the only ingredient that comes from an animal or human source. It has been confirmed that the lactose used to produce lactose monohydrate is sourced from healthy animals under the same conditions as milk for human consumption.

Pharmaceutical development
The objective of the pharmaceutical development programme was to produce products with 10mg and 25mg nortriptyline hydrochloride that are tolerable and can be considered as generic products to the originator products Allegron 10 and 25mg Tablets (King Pharmaceuticals Limited).

The rationale for the type of pharmaceutical form developed and formulation variables evaluated during development have been stated and are satisfactory.

The rationale and function of each excipient added is discussed. Levels of each ingredient are typical for a product of this nature and have been optimised on the basis of results from development studies.

Comparative in vitro dissolution and impurity profiles have been generated for the proposed and originator products, with satisfactory results.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the products along with an appropriate account of the manufacturing process. The manufacturing process has shown satisfactory results on validation batches.

Finished Product Specification
The finished product specifications proposed for both strengths are acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container-Closure System
All strengths of tablet are packaged in white high-density polyethylene bottles, with a child-resistant cap and tamper-evident film, in pack sizes of 100 tablets.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the relevant regulations regarding materials for use in contact with food.
Stability of the Product
Stability studies were performed on batches of all strengths of finished product in accordance with current guidelines. The results support a shelf-life of 48 months for both strengths, with the storage conditions “Do not store above 25°C. Store in original container. Keep the container tightly closed”.

Bioequivalence/Bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study. Bio-analytical methods used have been satisfactorily validated. Satisfactory bioequivalence is seen between the test and reference product (see Clinical Assessment).

Expert Report
A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

Summary of Product Characteristics
These are consistent with those for the reference products and are satisfactory.

Labelling
These are satisfactory

Patient Information Leaflet
This is consistent with that for the reference products and is satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA Forms
These are satisfactory.

Conclusion
It is recommended that marketing authorisations are granted for these applications.

The requirements for essential similarity of the proposed and reference products have been met with respect to qualitative and quantitative content of the active substance. In addition, similar dissolution and impurity profiles have been provided for the proposed and reference products.
PRECLINICAL ASSESSMENT

These applications are for generic medicinal products of Allegron 10 and 25mg Tablets (King Pharmaceuticals Limited), which have been licensed within the EEA for over 10 years.

No new preclinical data have been supplied with these applications and none are required for applications of this type.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
To support the applications, a bioequivalence study performed using the 25mg tablet formulation has been performed.

Efficacy Studies
No new efficacy data have been submitted and none are required for these generic applications.

Bioequivalence Study (25mg): a randomized, single-dose, open-label, crossover study, comparing the pharmacokinetic profiles of Nortriptyline 25mg Tablets (Test) versus Allegron 25mg Tablets (Reference) in healthy male subjects under fasted conditions.

Dosing occurred after a 10-hour fast, with standardised meals at 4, 9 and 13 hours post dose. Blood samples for pharmacokinetic analysis were taken pre- and up to 168 hours post dose. The results for both nortriptyline and its active metabolite (10-hydroxynortriptyline) are presented below:

### Nortriptyline:

<table>
<thead>
<tr>
<th></th>
<th>Geometric means</th>
<th>Ratio T/R</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test</td>
<td>Reference</td>
<td>% Lower Upper</td>
</tr>
<tr>
<td>AUC(0-t) ng.h/ml</td>
<td>276.526</td>
<td>272.43</td>
<td>101.50 92.94</td>
</tr>
<tr>
<td>AUC(0-∞) ng.h/ml</td>
<td>366.722</td>
<td>361.356</td>
<td>101.09 88.78</td>
</tr>
<tr>
<td>C\text{max} ng/ml</td>
<td>9.731</td>
<td>10.01</td>
<td>97.21 90.64</td>
</tr>
</tbody>
</table>

For both the active substance and its metabolite, the 90% confidence intervals lie between the acceptance criteria stated in the Notes for Guidance on Investigation of Bioavailability and Bioequivalence. Thus, bioequivalence has been shown between the test and reference products.

As the 10mg and 25mg products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 25mg strength can be extrapolated to the 10mg strength tablets also.

### EFFICACY
No new data have been provided and none are required.
SAFETY
No new data have been provided and none are required.

EXPERT REPORTS
A clinical expert report has been written by a suitably qualified person and is satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
These are consistent with those for the reference products and are satisfactory.

PATIENT INFORMATION LEAFLETS (PIL)
These are consistent with the SPC and are satisfactory.

LABELLING
These are satisfactory

APPLICATION FORMS (MAA)
These are satisfactory.

DISCUSSION
Bioequivalence has been satisfactorily demonstrated for the 10mg and 25mg products, in accordance with CPMP criteria.

MEDICAL CONCLUSION
The grant of marketing authorisations is recommended for these applications.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Nortriptyline 10mg and 25mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s 25mg strength tablets the reference product Allegron 25mg Tablets. As the 10mg and 25mg products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 25mg strength can be extrapolated to the 10mg strength tablets also.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those for the reference products, where necessary.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence studies support the claim that the applicant’s products and the innovator products are interchangeable. Extensive clinical experience with nortriptyline hydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
## NORTRIPTYLINE 10MG TABLETS
## NORTRIPTYLINE 25MG TABLETS

### STEPS TAKEN FOR ASSESSMENT

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The MHRA received the Marketing Authorisation applications on 3rd November 2006</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant, the MHRA considered the applications valid on 26th January 2007</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 28th October 2007, 8th April 2008, 19th December 2008 and 27th February 2009 for the quality sections, and 28th October 2007 for the clinical sections.</td>
</tr>
<tr>
<td>5</td>
<td>The applications were determined on 1st May 2009</td>
</tr>
</tbody>
</table>
NORTRIPTYLINE 10MG TABLETS
NORTRIPTYLINE 25MG TABLETS

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1 NAME OF THE MEDICINAL PRODUCT
Nortriptyline 10mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains nortriptyline hydrochloride equivalent to nortriptyline 10mg
The tablet also contains lactose monohydrate.
For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Tablet
White to off-white round biconvex tablets plain on both sides.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Nortriptyline is indicated for the relief of symptoms of depression. It may also be used for the
treatment of some cases of nocturnal enuresis.

4.2 Posology and method of administration
For oral administration

Adults: The usual adult dose is 25mg three or four times daily. Dosage should begin at a low
level and be increased as required. Alternatively, the total daily dose may be given once a day.
When doses above 100mg daily are administered, plasma levels of nortriptyline should be
monitored and maintained in the optimum range of 50 to 150ng/ml. Doses above 150mg per
day are not recommended.

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

If a patient develops minor side-effects, the dosage should be reduced. The drug should be
discontinued promptly if adverse effects of a serious nature or allergic manifestations occur.

Elderly: 30 to 50mg/day in divided doses.

Adolescent patients: 30 to 50mg/day in divided doses.

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

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

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

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Weight</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>kg</td>
<td>lb</td>
</tr>
<tr>
<td>6-7</td>
<td>20-25</td>
<td>44-55</td>
</tr>
<tr>
<td>8-11</td>
<td>25-35</td>
<td>55-77</td>
</tr>
<tr>
<td>&gt;11</td>
<td>35-54</td>
<td>77-119</td>
</tr>
</tbody>
</table>

The dose should be administered thirty minutes before bedtime.

The maximum period of treatment should not exceed three months. A further course of treatment should not be started until a full physical examination, including an ECG, has been made.

4.3 Contraindications

- Hypersensitivity to nortriptyline
- Recent myocardial infarction, any degree of heart block or other cardiac arrhythmias
- Severe liver disease
- Mania

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

Please also refer to 'Drug interactions' section.

4.4 Special warnings and precautions for use

Warnings: As improvement may not occur during the initial weeks of therapy, patients, especially those posing a high suicidal risk, should be closely monitored during this period.

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 especially 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 chlorpropanamide (250mg/day), after the addition of nortriptyline (125mg/day).

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

Barbiturates may increase the rate of metabolism of nortriptyline.

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

Tricyclic antidepressants may potentiate the CNS depressant effect of alcohol.

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

Steady-state serum concentrations of the tricyclic antidepressants are reported to fluctuate significantly as cimetidine is either added to or deleted from the drug regimen. Higher than expected steady-state serum concentrations of the tricyclic antidepressant have been observed when therapy is initiated in patients already taking cimetidine. A decrease may occur when cimetidine therapy is discontinued.
Because nortriptyline's metabolism (like other tricyclic and SSRI antidepressants) involves the hepatic cytochrome P450IID6 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 (416 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 (e.g. quinidine), should be approached with caution.

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

4.6 Pregnancy and lactation

Usage in 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.

Usage in nursing mothers: See 'Contra-indications'.

4.7 Effects on ability to drive and use machines

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

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.

The following definitions are usually used to evaluate side effects:

<table>
<thead>
<tr>
<th>Very common: More than 1 out of 10 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common: More than 1 but less than 10 out of 100 patients</td>
</tr>
<tr>
<td>Uncommon: More than 1 but less than 10 out of 1,000 patients</td>
</tr>
<tr>
<td>Rare: More than 1 but less than 10 out of 10,000 patients</td>
</tr>
<tr>
<td>Very rare: Less than 1 out of 10,000 patients</td>
</tr>
</tbody>
</table>

Very common: More than 1 out of 10 patients.

Dry mouth, sweating, constipation, blurred vision, and irregular or heavy heart beats.

Common: More than 1 but less than 10 out of 100 patients.

Strange body movements and headaches, blurred vision, sweating, flushing, weakness, fatigue, headache, high or low blood pressure, tremors.

Uncommon: More than 1 but less than 10 out of 1,000 patients.

Dizziness, changes in sleep patterns (including nightmares), numbness, nausea (feeling sick) & vomiting, problems urinating (increased or decreased) are all uncommon side effects.

Tingling in arms & legs, loss of appetite diarrhoea liver problems including jaundice, weight gain or loss & changes in sexual performance may also rarely occur.

Rare: More than 1 but less than 10 out of 10,000 patients.

Peculiar taste, mouth or gum problems, confusional states (especially in the elderly) perhaps with anxiety & restlessness are rare side effects. More serious heart problems along with ringing in the ears, stomach cramps and clumsiness can also occasionally occur. Some patients
have had a rash, which may be itchy or get worse in sunlight. If you suddenly stop taking the tablets, you may not be able to sleep and may feel irritable or sweaty.

*Very rare:* Less than 1 out of 10,000 patients.

Alterations in brain function (including perhaps seizures), swelling of ankles and in severe cases of the face & tongue. Blood disorders may also very rarely occur along with changes in blood sugar level. In severe cases men may suffer from swelling of breasts & testicles whilst women may also notice an increase in breast size and spontaneous lactation. In extreme cases there may be swelling & damage to liver cells.

*Frequency Unknown:* Cases of suicidal ideation and suicidal behaviours have been reported during nortriptyline therapy or early treatment discontinuation (see Section 4.4).

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

### 4.9 Overdose

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 Pharmacodynamic properties

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

In the treatment of depression Nortriptyline is given by mouth as the hydrochloride in doses equivalent to Nortriptyline 10mg 3 or 4 times daily initially, gradually increased to 25mg 4 times daily as necessary. A suggested initial dose for adolescents and the elderly is 10mg 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.
5.2 Pharmacokinetic properties
Parts of metabolism of Nortriptyline include hydroxylation (possibly to active metabolites), N-oxidation 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.

5.3 Preclinical safety data
Not relevant

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate
Maize Starch
Magnesium stearate

6.2 Incompatibilities
None Stated.

6.3 Shelf life
48 months.

6.4 Special precautions for storage
Do not store above 25°C. Store in original container. Keep the container tightly closed.

6.5 Nature and contents of container
Tablets are packed in a white HDPE bottle, with a white polypropylene child resistant cap and tamper evident film, containing 100 tablets

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORITY
NRIM Limited
Marlborough House
298, Regents Park Road
Finchley N3 2UA
London, United Kingdom

8 MARKETING AUTHORIZATION NUMBER(S)
PL 20620/0018

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
01/05/2009

10 DATE OF REVISION OF THE TEXT
01/05/2009
1 NAME OF THE MEDICINAL PRODUCT
Nortriptyline 25mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains nortriptyline hydrochloride equivalent to nortriptyline 25mg
The tablet also contains lactose monohydrate.
For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Tablet
White to off-white round biconvex tablets plain on both sides.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Nortriptyline is indicated for the relief of symptoms of depression. It may also be used for the
treatment of some cases of nocturnal enuresis.

4.2 Posology and method of administration
For oral administration

Adults: The usual adult dose is 25mg three or four times daily. Dosage should begin at a low
level and be increased as required. Alternatively, the total daily dose may be given once a day.
When doses above 100mg daily are administered, plasma levels of nortriptyline should be
monitored and maintained in the optimum range of 50 to 150ng/ml. Doses above 150mg per
day are not recommended.

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

If a patient develops minor side-effects, the dosage should be reduced. The drug should be
discontinued promptly if adverse effects of a serious nature or allergic manifestations occur.

Elderly: 30 to 50mg/day in divided doses.

Adolescent patients: 30 to 50mg/day in divided doses.

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

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

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

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Weight</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-7</td>
<td>20-25</td>
<td>10</td>
</tr>
<tr>
<td>8-11</td>
<td>25-35</td>
<td>10-20</td>
</tr>
<tr>
<td>&gt;11</td>
<td>35-54</td>
<td>25-35</td>
</tr>
</tbody>
</table>

The dose should be administered thirty minutes before bedtime.

The maximum period of treatment should not exceed three months. A further course of treatment should not be started until a full physical examination, including an ECG, has been made.

4.3 Contraindications

- Hypersensitivity to nortriptyline
- Recent myocardial infarction, any degree of heart block or other cardiac arrhythmias
- Severe liver disease
- Mania

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

Please also refer to 'Drug interactions' section.

4.4 Special warnings and precautions for use

**Warnings:** As improvement may not occur during the initial weeks of therapy, patients, especially those posing a high suicidal risk, should be closely monitored during this period.

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 especially 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 Interaction with other medicinal products and other forms of interaction

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

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

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

Barbiturates may increase the rate of metabolism of nortriptyline.

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

Tricyclic antidepressants may potentiate the CNS depressant effect of alcohol.

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

Steady-state serum concentrations of the tricyclic antidepressants are reported to fluctuate significantly as cimetidine is either added to or deleted from the drug regimen. Higher than expected steady-state serum concentrations of the tricyclic antidepressant have been observed when therapy is initiated in patients already taking cimetidine. A decrease may occur when cimetidine therapy is discontinued.
Because nortriptyline's metabolism (like other tricyclic and SSRI antidepressants) involves the hepatic cytochrome P450IID6 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 (416 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 (e.g. quinidine), should be approached with caution.

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

4.6 Pregnancy and lactation

Usage in 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.

Usage in nursing mothers: See 'Contra-indications'.

4.7 Effects on ability to drive and use machines

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

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.

The following definitions are usually used to evaluate side effects:

| Very common: More than 1 out of 10 patients |
| Common: More than 1 but less than 10 out of 100 patients |
| Uncommon: More than 1 but less than 10 out of 1,000 patients |
| Rare: More than 1 but less than 10 out of 10,000 patients |
| Very rare: Less than 1 out of 10,000 patients |

Very common: More than 1 out of 10 patients.

Dry mouth, sweating, constipation, blurred vision, and irregular or heavy heart beats.

Common: More than 1 but less than 10 out of 100 patients.

Strange body movements and headaches, blurred vision, sweating, flushing, weakness, fatigue, headache, high or low blood pressure, tremors.

Uncommon: More than 1 but less than 10 out of 1,000 patients.

Dizziness, changes in sleep patterns (including nightmares), numbness, nausea (feeling sick) & vomiting, problems urinating (increased or decreased) are all uncommon side effects.

Tingling in arms & legs, loss of appetite diarrhoea liver problems including jaundice, weight gain or loss & changes in sexual performance may also rarely occur.

Rare: More than 1 but less than 10 out of 10,000 patients.

Peculiar taste, mouth or gum problems, confusional states (especially in the elderly) perhaps with anxiety & restlessness are rare side effects. More serious heart problems along with ringing in the ears, stomach cramps and clumsiness can also occasionally occur. Some patients
have had a rash, which may be itchy or get worse in sunlight. If you suddenly stop taking the tablets, you may not be able to sleep and may feel irritable or sweaty.

Very rare: Less than 1 out of 10,000 patients.
Alterations in brain function (including perhaps seizures), swelling of ankles and in severe cases of the face & tongue. Blood disorders may also very rarely occur along with changes in blood sugar level. In severe cases men may suffer from swelling of breasts & testicles whilst women may also notice an increase in breast size and spontaneous lactation. In extreme cases there may be swelling & damage to liver cells.

Frequency Unknown: Cases of suicidal ideation and suicidal behaviours have been reported during nortriptyline therapy or early treatment discontinuation (see Section 4.4).

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

4.9 Overdose

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 alkalisation 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 Pharmacodynamic properties

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

In the treatment of depression Nortriptyline is given by mouth as the hydrochloride in doses equivalent to Nortriptyline 10mg 3 or 4 times daily initially, gradually increased to 25mg 4 times daily as necessary. A suggested initial dose for adolescents and the elderly is 10mg 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.
5.2 Pharmacokinetic properties
Parts of metabolism of Nortriptyline include hydroxylation (possibly to active metabolites), N-oxidation 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.

5.3 Preclinical safety data
Not relevant

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate
Maize Starch
Magnesium stearate

6.2 Incompatibilities
None Stated.

6.3 Shelf life
48 months.

6.4 Special precautions for storage
Do not store above 25°C. Store in original container. Keep the container tightly closed.

6.5 Nature and contents of container
Tablets are packed in a white HDPE bottle, with a white polypropylene child resistant cap and tamper evident film, containing 100 tablets

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
NRIM Limited
Marlborough House
298, Regents Park Road
Finchley N3 2UA
London, United Kingdom

8 MARKETING AUTHORIZATON NUMBER(S)
PL 20620/0019

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
01/05/2009

10 DATE OF REVISION OF THE TEXT
01/05/2009
NORTRIPTYLINE 10MG & 25MG TABLETS

PATIENT INFORMATION LEAFLET

READ ALL OF THIS LEAFLET CAREFULLY BEFORE YOU START USING THIS MEDICINE.

- Keep this leaflet, you may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

THE LEAFLET CONTAINS INFORMATION ON:
1. What Nortriptyline Tablets are and what they are used for.
2. Before you take Nortriptyline Tablets.
3. How to take Nortriptyline Tablets.
4. Possible side effects.
5. How to store Nortriptyline Tablets.
6. Further information.

1. WHAT IS NORTRIPTYLINE TABLETS AND WHAT IS IT USED FOR?

Nortriptyline belongs to a class of medicines called tricyclic antidepressants. Antidepressants are used to:
- Reduce the symptoms of depression.
- Help stop children bed-wetting.

2. BEFORE YOU TAKE NORTRIPTYLINE TABLETS

You should not take Nortriptyline Tablets until you are sure it is safe for you to do so. Nortriptyline Tablets are only to be given to children if they are over the age of 6 and it is given to help them stop bed-wetting.

Do not take Nortriptyline Tablets if you:
- Have had a rash or any other allergic reaction to Nortriptyline or to any other tricyclic antidepressant.
- Have recently had a heart attack or do you have other heart problems such as palpitations or irregular heartbeats?
- Have ever had problems with your liver?
- Have ever had mania or schizoaffective?
- Are a nursing mother.
- Are under six years of age.

Take special care with Nortriptyline Tablets.
- Do not take Nortriptyline Tablets without discussing with your doctor if you:
  - Are having an operation under general anaesthetic discuss this with your GP. You may need to stop taking Nortriptyline Tablets several days before the operation. If your GP tells you to carry on taking Nortriptyline Tablets, make sure the doctors treating you in hospital know that you are on Nortriptyline.
  - Are pregnant or may be pregnant.
  - Have thyroid problem.
  - Ever had epilepsy.
  - Are diabetic.

Do not take Nortriptyline Tablets if the above apply to you. If you are not sure, talk to your doctor or pharmacist.

Thoughts of suicide and worsening of your depression or anxiety disorder

If you are depressed and/or have anxiety disorders you can sometimes have thoughts of harming or killing yourself. These may be increased when first starting antidepressants, since these medicines all take time to work, usually about two weeks but sometimes longer. You may be more likely to think about this:
- If you have previously had thoughts about harming or killing yourself.
- If you are a young adult. Information from clinical trials has shown an increased risk of suicidal behaviour in adults aged less than 25 years with psychiatric conditions who were treated with an antidepressant.

If you have thoughts of harming or killing yourself at any time contact your doctor or go to a hospital straight away.

You may find it helpful to talk to a relative or close friend if you are depressed or have an anxiety disorder, and ask them to read this leaflet. You might ask them to tell you if they think your depression or anxiety is getting worse, or if they are worried about changes in your behaviour.

Taking other medicines

You should not take Nortriptyline Tablets without discussing with your doctor if you:
- Are taking, or you have recently been taking, any medicines known as monoamine oxidase inhibitors (MAOIs). MAOIs include phenelzine such as Sansert, tranylcypromine such as Parnate, isocarboxazid such as Marplan. Tell your doctor or pharmacist if you are taking them now or have taken them in the last 2 weeks.
- Are taking any medicines for your heart or for high blood pressure.
- Ever use cough or cold remedies.
- Are taking cyclobenzaprine, such as Tegamet.
- Are taking any other medicines, including other antidepressants or medicine for bowel complaints, breathing difficulties, bronchitis, glaucoma or prostate trouble?

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines including medicines obtained with or without a prescription.

Taking Nortriptyline Tablets with food and drink.

You should not drink alcohol while you are being treated with Nortriptyline Tablets. You may find that you get more drunk or feel more depressed.

Use by pregnant or breast-feeding women

The safety of nortriptyline for use during pregnancy has not been established. Hence, it should be taken only if your doctor advises to do so. Please ask your doctor or pharmacist for advice before taking any medicine.

You should not take Nortriptyline Tablets if you are breast-feeding.

Driving and using machines:

Do not drive or use machinery when you are on nortriptyline Tablets unless you are sure your judgement and co-ordination are not affected. Antidepressants may affect your ability to drive or to operate machinery safely.

Important information about some of the ingredients of Nortriptyline Tablets

Nortriptyline Tablets contain lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
UKPAR Nortriptyline 10mg and 25mg Tablets

PL 20620/0018-9

1. HOW TO TAKE NORTRIPTYLINE TABLETS

Always take Nortriptyline tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are unsure.

Adults

Dose will be taken in either 2, 3 or 4 doses. You will usually be told to increase your dose gradually until you are taking 75 mg to 100mg a day if you are elderly or a teenager. You will usually be told to take one 10mg tablets a times a day.

If you feel better, you may be told to carry on taking Nortriptyline tablets but to take a lower dose.

Do not take more than six 25mg tablets a day (150mg).

If your doctor tells you to take more than four 25mg tablets a day, he or she may arrange for you to have regular blood tests.

Antidepressants may not make you feel better for the first two weeks or more of treatment, so keep taking Nortriptyline tablets until your doctor tells you to stop. Do not stop these tablets without discussing it with your doctor first.

Do not suddenly stop taking the tablets. Your doctor will tell you how to cut them down gradually.

Children

The usual dose for children depends on the child’s age and weight. Give your child the tablets half an hour before bedtime. Children should not take Nortriptyline Tablets for longer than three months.

Swallow the tablets with water.

If you are unsure about how many tablets to take, or how many to give a child, ask your doctor or pharmacist.

If you take more Nortriptyline Tablets than you should do not take more tablets than your doctor tells you to. If you feel any side effects, or if you have taken too many tablets, go to the nearest hospital casualty department or call your doctor at once. An overdose can be very dangerous.

If you forget to take Nortriptyline Tablets if you forget to take a dose, take it as soon as you remember. If it is almost time for your next dose do not take a double dose to make up for a forgotten dose, just carry on as before. If you have missed several doses, discuss this with your doctor.

If you stop using Nortriptyline Tablets

If you stop using Nortriptyline Tablets abruptly after prolonged therapy you may have withdrawal symptoms, including not being able to sleep, and may feel irritable or sweaty.

4. POSSIBLE SIDE EFFECTS

Like all medicines Nortriptyline can cause side effects although not everybody gets them.

Tell your doctor or pharmacist immediately if you experience any of the following:

- Serious heart problems along with ringing in the ears, stomach cramps and dizziness.
- Swelling of ankles and in severe cases of the face & tongue.
- Alterations in brain function (including paranoia).
- Blood disorders along with changes in blood sugar level.
- Swelling of breasts & testicles in men and increase in breast size and spontaneous lactation in women.
- Swelling & damage to liver cells.

The following side effects have also been reported:

Very common: More than 1 in 10 of patients.

- Dry mouth, sweating, constipation, blurred vision, irregular

Common: More than 1 but less than 10 out of 100 patients.

- Changes in body movements and headaches, blurred vision,

Uncommon: More than 1 but less than 10 out of 100 patients.

- Dizziness, changes in sleep patterns (including nightmares), numbness, nausea (feeling sick) & vomiting.

Rare: More than 1 but less than 10 out of 10,000 patients.

- Peripheral taste, mouth or gum problems, confusion.

Very rare: Less than 1 out of 10,000 patients.

- Allergies in brain function (including perhaps sensitivity to sunlight), swelling of ankles and in severe cases of the face & tongue.

5. HOW TO STORE NORTRIPTYLINE TABLETS

- Keep out of the reach of children.
- Do not use Nortriptyline Tablets after the expiry date, which is stated on the label and carton. The expiry date refers to the last day of the month shown on the label.
- Do not store above 25°C. Store in the original container.
- Keep the container tightly closed.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Nortriptyline Tablets contain?

The name of this medicine is Nortriptyline 10mg or 25mg Tablets.

The active substance in your tablet is nortriptyline hydrochloride. Each tablet contains 10mg or 25mg of nortriptyline (as the hydrochloride) respectively. Other ingredients include Lactose monohydrate, maize starch and magnesium stearate.

What Nortriptyline Tablets look like and contents of the pack

Nortriptyline 10mg Tablets are white to off white, round, biconvex, uncoated tablets, embossed 'NM' on one side and '10' on other side.

Nortriptyline 25mg Tablets are white to off white, round, biconvex, uncoated tablets, embossed 'NM' on one side and '25' on other side.

Nortriptyline 10mg & 25mg Tablets are packed in a white HDPE bottle, with a white polypropylene child resistant cap and tamper evident foil, containing 100 tablets.

Marketing Authorisation Holder and Manufacturer

The Marketing Authorisation holder and manufacturer of these tablets is NPS Medicine, 196 Regents Park Road, Finchley, London, N3 2UA, United Kingdom.

This leaflet was prepared in 02/2009.