Public Assessment Report
Mutual Recognition Procedure

Nortriptyline 10mg Tablets
Nortriptyline 25mg Tablets

(Nortriptyline hydrochloride)

UK/H/4130/001-2/MR
UK Licence No: PL 20620/0018-9

NRIM Limited
NORTRIPTYLINE 10MG TABLETS
NORTRIPTYLINE 25MG TABLETS

LAY SUMMARY

On 1st May 2009, the UK granted NRIM Limited Marketing Authorisations (licences) for the medicinal products Nortriptyline 10mg and 25mg Tablets.

Based on the review of the data on quality, safety and efficacy, Germany, Italy, the Netherlands, Spain considered that the applications for Nortriptyline 10mg and 25mg Tablets could be approved.

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

These are prescription only medicines (POM) to treat major depression.

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 these Marketing Authorisations have been granted.
NORTRIPTYLINE 10MG TABLETS
NORTRIPTYLINE 25MG TABLETS

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2 Quality aspects
3 Non-clinical aspects
4 Clinical aspects
5 Overall conclusions

Module 6: Steps taken after initial procedure  Not applicable
Module 1

| **Product Names** | Nortriptyline 10mg Tablets  
Nortripsyline 25mg Tablets |
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<tr>
<td><strong>Type of Application</strong></td>
<td>Generic application, Article 10(1)</td>
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<td><strong>Active Substance</strong></td>
<td>Nortriptyline hydrochloride</td>
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<td><strong>Pharmaceutical Form</strong></td>
<td>Tablets</td>
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| **Strengths** | 10mg  
25mg |
| **MA Holder** | NRIM Limited  
Unit 15 Moorcroft,  
Harlington Road,  
Hillingdon,  
UB8 3HD  
UK |
| **Reference Member State (RMS)** | UK |
| **Concerned Member States (CMS)** | Germany (DE), Italy (IT), the Netherlands (NL) and Spain (ES) |
| **Procedure Numbers** | UK/H/4130/001/MR  
UK/H/4130/002/MR |
| **End of Procedure** | Day 90 – 24th January 2011 |
Module 2
Summary of Product Characteristics

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 treatment of Major Depressive Episodes.

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
(50mg once daily or 25mg 2-3 times daily). If necessary, dose could be gradually increased in 25mg
increments no more than rapidly than every other day to be added to the morning dose. When doses
above 100mg daily are administered, monitoring of plasma levels of nortriptyline should be considered
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. 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. The maintenance dose should be the same as the optimal therapeutic dose.
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. Dosage should begin at a low level (10 – 20 mg daily) and
be increased as required to the maximum dose of 50mg. If it is considered necessary to use higher
dosing in an elderly patient an ECG should be checked and plasma levels of nortriptyline should be
monitored.

Adolescent patients: The use of nortriptyline in children and adolescents to treat depression is not
recommended due to lack of evidence regarding its safety and efficacy.
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, 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 cardio toxicity,
despite the fact that nortriptyline concentrations were within the ‘therapeutic range’. Clinical findings
should predominate over plasma concentrations as primary determinants of dosage changes.
A lower or less frequent dose should be considered in patients with hepatic impairment, concurrent
diseases, or who are taking multiple medications (see “4.4 Special Warnings and Precautions for Use”
and “4.5 interactions with other Medicinal products and other forms of Interaction”)

5
Renal failure does not affect the kinetics of nortriptyline.

**Duration of treatment:** The antidepressive effect usually sets in after 2-4 weeks. Treatment with antidepressants is symptomatic and should therefore be continued for a sufficient period of time, usually 6 months or longer to prevent recurrence.

**Discontinuation:** Treatment should be discontinued gradually, otherwise withdrawal symptoms as headache, sleep disturbances, irritability and malaise could develop. These symptoms are not indicative of addiction.

### 4.3 CONTRAINDICATIONS

- Hypersensitivity to nortriptyline
- Recent myocardial infarction, any degree of heart block or other cardiac arrhythmias
- As for all tricyclic antidepressants, nortriptyline should not be administered to patients who are treated with monoamine oxidase inhibitors (MAOIs; e.g., phenelzine, tranylcypromine, etc.). Concomitant use of nortriptyline and a MAOI might cause serotonin syndrome (a syndrome that can include symptoms such as agitation, confusion, tremor, myoclonia en hyperthermia). Nortriptyline therapy can begin 14 days after the termination of a MAOI, and 1 day after the termination of the reversible MAOI moclobemide. Treatment with MAOIs can begin 14 days after the terminations of treatment with nortriptyline (see section 4.5).

Please also refer to 'Drug interactions' section.

### 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

#### Use in children and adolescents under the age of 18

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 (SSRI’s and SNRI’s) 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 (see also section 4.8 Undesirable effects and Section 4.9 Overdose.)

**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.

**Suicide/suicidal thoughts or clinical worsening:** Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery. Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy 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, nausea, headache 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. Caution should be exercised when treating patients with advanced liver disease. Patients with cardiovascular disease or hypotension 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. Arrhythmias and
hypotension can occur in patients without prior risk, especially when high doses are prescribed. Therefore patients who receive high doses should be followed up for arrhythmia’s and hypotension. 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, other anti-cholinergic reactions and postural hypotension.

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

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.

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).

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

In patients developing throat pain, fever and flu symptoms during the first 10 weeks of treatment, it is recommended that a FBC is taken 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.

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

Barbiturates may increase the rate of metabolism of nortriptyline.

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

Tricyclic antidepressants may potentiate the CNS depressant effect of alcohol. The potentiating effect of excessive consumption of alcohol may lead to increased suicidal attempts or overdose, especially in patients with histories of emotional disturbances or suicidal ideation.

Steady-state serum concentrations of the tricyclic antidepressants are reported to fluctuate significantly as cimetidine is either added to or deleted from the drug regimen. Higher than expected steady-state serum concentrations of the tricyclic antidepressant have been observed when therapy is initiated in patients already taking cimetidine. A decrease may occur when cimetidine therapy is discontinued. Because nortriptyline's metabolism (like other tricyclic and SSRI antidepressants) involves the hepatic cytochrome P450IID6 isoenzyme system, concomitant therapy with drugs also metabolised by this system may lead to drug interactions. Lower doses than are usually prescribed for either the tricyclic antidepressant or the other drug may therefore be required.

Greater than two-fold increases in previously stable plasma levels of nortriptyline have occurred when fluoxetine was administered concomitantly. Fluoxetine and its active metabolite, norfluoxetine, have long half-lives (4-16 days for norfluoxetine).
Concomitant therapy with other drugs that are metabolised by this isoenzyme, including other antidepressants, phenothiazines, carbamazepine, propafenone, flecainide and encainide, or that inhibit this enzyme (e.g. quinidine), should be approached with caution. 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, halofrantrine, and sotalol can increase the risk for ventricular arrhythmia’s in combination with TCA’s. TCAs have some characteristics of class I anti-arrhythmics. 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 anti-arrhythmics and loop and thiazide diuretics attention should be paid to potential inhibitory effect on the QT time due to potassium loss. Antifungal medication such as fluconazol and terbinafine increase the serum concentration of tricyclic antidepressants and the associated toxicity. Syncope and Torsade de Pointes have been reported. In combination with levodopa 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. TCAs may increase the risk of seizure in patients using tramadol. The “serotonin syndrome” (changes in cognition, behaviour, function of the autonomic nervous system and neuromuscular activity) have been reported when nortriptyline is administered together with serotonin enhancing medications. 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.

4.6 PREGNANCY AND LACTATION

Usage in pregnancy: A moderate amount of data in pregnant women indicate no malformative or feto/neonatal toxicity. Animal studies have shown reproductive toxicity (see section 5.3). Nortriptyline should only be used when strictly indicated.

The kinetics of nortriptyline changes during pregnancy, especially during the 2nd and 3rd trimesters. Therefore serum levels should be monitored and the dose should be adjusted if needed. After chronic use and administration near term neonatal withdrawal symptoms (irritability, hypertonia, tremors, irregular breathing, weak suckling) and anticholinergic symptoms (urine retention, constipation) may occur.

Usage in Lactation: Nortriptyline is excreted in limited amounts. The relative infant dose is low and serum levels have been reported as low or undetectable. Adverse effects on the sucking infant have not been reported to date. Nortriptyline can be used during lactation if the expected benefit for the mother outweighs the potential risk to the infant. 

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.

Examinations:
Common: weight increase, abnormal ECG, QT prolongation, QRS complex prolongation
Uncommon: increased intraocular pressure
Rare: weight loss, abnormal liver function, increased blood alkaline phosphatase, increased transaminase
Very rare: changes in blood sugar levels
Cardiovascular:
*Very common:* palpitation, irregular or heavy heart beats and tachycardia
*Common:* atrioventricular block, bundle branch block, high or low blood pressure
*Rare:* arrhythmias
*Very rare:* peripheral oedema

Blood and Lymphatic disorders:
*Rare:* bone marrow depression, agranulocytosis, leucopenia, eosinophilia, thrombocytopenia

Nervous system disorders:
*Very common:* dizziness, headache
*Common:* concentration disorders, taste disorders, paraesthesia, ataxia, strange body movements and tremors.
*Uncommon:* convulsion, numbness
*Rare:* clumsiness
*Very rare:* Alterations in brain function (including perhaps seizures)

Eye disorders:
*Very common:* accommodation disorder including blurred vision
*Common:* mydriasis

Vestibular and ear disorders:
*Uncommon:* tinnitus

Gastrointestinal disorders:
*Very common:* dry mouth, constipation
*Uncommon:* diarrhoea, nausea, vomiting, tongue oedema
*Rare:* increased salivary glands, paralytic ileus, loss of appetite, diarrhoea, and stomach cramps

Kidney and urinary tract disorders:
*Uncommon:* problems urinating (increased or decreased) and urinary retention

Skin and subcutaneous disorders:
*Very common:* sweating, flushing
*Uncommon:* rash, urticaria, facial oedema
*Rare:* alopecia, light sensitivity

Endocrine disorders:
Unknown: SIADH

Nutritional and metabolic disorders:
*Rare:* decreased appetite, weight gain or loss

Vascular diseases:
*Very common:* orthostatic hypotension
*Uncommon:* hypertension

General and application site disorders:
*Common:* weakness and fatigue,
*Rare:* fever, peculiar taste, mouth or gum problems,

Liver and bile disorders:
*Rare:* Jaundice
Unknown: cholestasis

Reproductive system and breast disorders:
*Common:* erection disorders
*Rare:* gynaecomastia, changes in sexual performance may also rarely occur.
*Very rare:* galactorrhoea, swelling of testicles

Psychiatric disorders:
*Common:* confusion, decreased libido
Uncommon: hypomania, mania, anxiety, insomnia (especially on sudden withdrawal), changes in sleep patterns (including nightmares)

Rare: confusional states / delirium (especially in older patients), hallucinations (in patients with schizophrenia), irritability

Unknown Cases of suicidal ideation and suicidal behaviours have been reported during nortriptyline therapy or early treatment discontinuation (see Section 4.4). Agitation, restlessness, aggressive outbursts, delusions, orgasm disorders in women, increased libido, disorientation

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

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

4.9 OVERDOSE

Individual differences in metabolism may lead to symptoms and signs of overdose even after relatively modest excess ingestion, irrespective of age.

Signs and symptoms: 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. Early transfer to a hospital with an intensive care unit is recommended. Activated charcoal may be more effective than emesis or lavage to reduce absorption, although combination therapy may be appropriate depending on the time since ingestion.

Ventricular arrhythmias, especially when accompanied by lengthened QRS intervals, may respond to alkalinisation by hyperventilation or administration of sodium bicarbonate or the rapid infusion of hypertonic sodium chloride (100-200mmol). Serum electrolytes should be monitored and managed. Refractory arrhythmias may respond to propranolol, bretylium or lignocaine (usually 1-1.5mg/kg iv followed by 1-3mg/min). Quinidine and procaainamide usually should not be used because they may exacerbate arrhythmias and conduction already slowed by the overdose.

Seizures or agitation 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.

Doses as low of 50mg (especially in children) may lead to clinically significant symptoms.

Cardiotoxicity and convulsions are commoner in children and toxicological advice is recommended in all cases.

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. Nortriptyline itself is a stronger inhibitor of pre-synaptic noradrenaline reuptake than of serotonin, and is less anticholinergic than amitriptyline whilst having stronger antihistaminergic effects.

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

Absorption: oral administration results in maximum plasma concentrations in approximately 5 hours (Tmax = 5.5 ±1.9 hours; range 4.0-8.8 hours). The mean oral bioavailability is 51% (Fabs = 0.51±0.05; range 0.46-0.59).

Distribution: The apparent volume of distribution (Vd)β, estimated after intravenous administration is 1633 ± 268 l; range 1460 to 2030 (21 ± 41 / 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 nortripyline 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 ½ β) after oral nortriptyline administration is approximately 26 hours (25.5 ± 7.9 hours; range 16-38 hours). The mean systemic clearance (Cls) is 30.6 ± 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. Pharmacokinetic / pharmacodynamic relationship

The therapeutic plasma concentration in endogenous depression is 50-140 ng / ml (~ 190-530 nmol / l). Levels above 170-200 ng/ml are associated with an increased risk of cardiac conduction disturbance in terms of a prolonged QRS complex or an AV block.

5.3 PRECLINICAL SAFETY DATA

Malformations have been observed in animal reproduction studies, in particular cranial malformations and encephalocoele.

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
Unit 15 Moorcroft,
Harlington Road,
Hillingdon,
UB8 3HD
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 20620/0018

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

10 DATE OF REVISION OF THE TEXT
10/11/2011
1 NAME OF THE MEDICINAL PRODUCT
Nortriptyline 25mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
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The tablet also contains lactose monohydrate.
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4 CLINICAL PARTICULARS
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Nortriptyline is indicated for the treatment of Major Depressive Episodes.

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 (50mg once daily or 25mg 2-3 times daily). If necessary, dose could be gradually increased in 25mg increments no more than rapidly than every other day to be added to the morning dose. When doses above 100mg daily are administered, monitoring of plasma levels of nortriptyline should be considered 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. 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. The maintenance dose should be the same as the optimal therapeutic dose. 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. Dosage should begin at a low level (10 – 20 mg daily) and be increased as required to the maximum dose of 50mg. If it is considered necessary to use higher dosing in an elderly patient an ECG should be checked and plasma levels of nortriptyline should be monitored.

**Adolescent patients:** The use of nortriptyline in children and adolescents to treat depression is not recommended due to lack of evidence regarding its safety and efficacy.
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. A lower or less frequent dose should be considered in patients with hepatic impairment, concurrent diseases, or who are taking multiple medications (see “4.4 Special Warnings and Precautions for Use” and “4.5 interactions with other Medicinal products and other forms of Interaction”)
Renal failure does not affect the kinetics of nortriptyline.

**Duration of treatment:** The antidepressive effect usually sets in after 2-4 weeks. Treatment with antidepressants is symptomatic and should therefore be continued for a sufficient period of time, usually 6 months or longer to prevent recurrence.
**Discontinuation:** Treatment should be discontinued gradually, otherwise withdrawal symptoms as headache, sleep disturbances, irritability and malaise could develop. These symptoms are not indicative of addiction.

### 4.3 CONTRAINDICATIONS
- Hypersensitivity to nortriptyline
- Recent myocardial infarction, any degree of heart block or other cardiac arrhythmias
- As for all tricyclic antidepressants, nortriptyline should not be administered to patients who are treated with monoamine oxidase inhibitors (MAOIs; e.g., phenelzine, tranylcypromine, etc.). Concomitant use of nortriptyline and a MAOI might cause serotonin syndrome (a syndrome that can include symptoms such as agitation, confusion, tremor, myoclonia en hyperthermia). Nortriptyline therapy can begin 14 days after the termination of a MAOI, and 1 day after the termination of the reversible MAOI moclobemide. Treatment with MAOIs can begin 14 days after the terminations of treatment with nortriptyline (see section 4.5).

Please also refer to 'Drug interactions' section.

### 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

#### Use in children and adolescents under the age of 18
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 (SSRI’s and SNRI’s) 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 (see also section 4.8 Undesirable effects and Section 4.9 Overdose.)

**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.

**Suicide/suicidal thoughts or clinical worsening:** Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

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

Close supervision of patients and in particular those at high risk should accompany drug therapy 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, nausea, headache 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.

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

Patients with cardiovascular disease or hypotension 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. Arrhythmias and hypotension can occur in patients without prior risk, especially when high doses are prescribed. Therefore patients who receive high doses should be followed up for arrhythmia’s and hypotension.

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, other anti-cholinergic reactions and postural hypotension.

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

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).

Adjustment of anti-diabetic therapy may, therefore, be necessary. In patients developing throat pain, fever and flu symptoms during the first 10 weeks of treatment, it is recommended that a FBC is taken 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.

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, methyl dopa and possibly clonidine. Concurrent administration of reserpine has been shown to produce a 'stimulating' effect in some depressed patients. It would be advisable to review all antihypertensive therapy during treatment with tricyclic antidepressants. Barbiturates may increase the rate of metabolism of nortriptyline.

Anaesthetics given during tricyclic antidepressant therapy may increase the risk of arrhythmias and hypotension. If surgery is necessary, the drug should be discontinued, if possible, for several days prior to the procedure, or the anaesthetist should be informed if the patient is still receiving therapy. Tricyclic antidepressants may potentiate the CNS depressant effect of alcohol. The potentiating effect of excessive consumption of alcohol may lead to increased suicidal attempts or overdose, especially in patients with histories of emotional disturbances or suicidal ideation. Steady-state serum concentrations of the tricyclic antidepressants are reported to fluctuate significantly as cimetidine is either added to or deleted from the drug regimen. Higher than expected steady-state serum concentrations of the tricyclic antidepressant have been observed when therapy is initiated in patients already taking cimetidine. A decrease may occur when cimetidine therapy is discontinued. Because nortriptyline's metabolism (like other tricyclic and SSRI antidepressants) involves the hepatic cytochrome P450IID6 isoenzyme system, concomitant therapy with drugs also metabolised by this system may lead to drug interactions. Lower doses than are usually prescribed for either the tricyclic antidepressant or the other drug may therefore be required. Greater than two-fold increases in previously stable plasma levels of nortriptyline have occurred when fluoxetine was administered concomitantly. Fluoxetine and its active metabolite, norfluoxetine, have long half-lives (4-16 days for norfluoxetine). Concomitant therapy with other drugs that are metabolised by this isoenzyme, including other antidepressants, phenothiazines, carbamazepine, propafenone, flecainide and encainide, or that inhibit this enzyme (e.g. quinidine), should be approached with caution. 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, halofranfine, and sotalol can increase the risk for ventricular arrhythmia’s in combination with TCA’s. TCAs have some characteristics of class I anti-arrhythmics. 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 anti-arrhythmias and loop and thiazide diuretics
attention should be paid to potential inhibitory effect on the QT time due to potassium loss.
Antifungal medication such as fluconazol and terbinafine increase the serum concentration of tricyclic
antidepressants and the associated toxicity. Syncope and Torsade de Pointes have been reported.
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.
TCAs may increase the risk of seizure in patients using tramadol.
The “serotonin syndrome” (changes in cognition, behaviour, function of the autonomic nervous system
and neuromuscular activity) have been reported when nortriptyline is administered together with
serotonin enhancing medications.
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.

4.6 PREGNANCY AND LACTATION
Usage in pregnancy: A moderate amount of data in pregnant women indicate no malformative or
feto/neonatal toxicity. Animal studies have shown reproductive toxicity (see section 5.3). Nortriptyline
should only be used when strictly indicated.

The kinetics of nortriptyline changes during pregnancy, especially during the 2nd and 3rd trimesters.
Therefore serum levels should be monitored and the dose should be adjusted if needed. After chronic
use and administration near term neonatal withdrawal symptoms (irritability, hypertonia, tremors,
irregular breathing, weak sucking) and anticholinergic symptoms (urine retention, constipation) may
occur.

Usage in Lactation: Nortriptyline is excreted in limited amounts. The relative infant dose is low and
serum levels have been reported as low or undetectable. Adverse effects on the suckling infant have not
been reported to date. Nortriptyline can be used during lactation if the expected benefit for the mother
outweighs the potential risk to the infant.”

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 |

Examinations:
Common: weight increase, abnormal ECG, QT prolongation, QRS complex prolongation
Uncommon: increased intraocular pressure
Rare: weight loss, abnormal liver function, increased blood alkaline phosphatase, increased
transaminase
Very rare: changes in blood sugar levels

Cardiovascular:
Very common: palpitation, irregular or heavy heart beats and tachycardia
Common: atrioventricular block, bundle branch block, high or low blood pressure
Rare: arrhythmias
Very rare: peripheral oedema
**Blood and Lymphatic disorders:**
*Rare:* bone marrow depression, agranulocytosis, leucopenia, eosinophilia, thrombocytopenia

**Nervous system disorders:**
*Very common:* dizziness, headache
*Common:* concentration disorders, taste disorders, paraesthesia, ataxia, strange body movements and tremors.
*Uncommon:* convulsion, numbness
*Rare:* clumsiness
*Very rare:* Alterations in brain function (including perhaps seizures)

**Eye disorders:**
*Very common:* accommodation disorder including blurred vision
*Common:* mydriasis

**Vestibular and ear disorders:**
*Uncommon:* tinnitus

**Gastrointestinal disorders:**
*Very common:* dry mouth, constipation
*Uncommon:* diarrhoea, nausea, vomiting, tongue oedema
*Rare:* increased salivary glands, paralytic ileus, loss of appetite, diarrhoea, and stomach cramps

**Kidney and urinary tract disorders:**
*Uncommon:* problems urinating (increased or decreased) and urinary retention

**Skin and subcutaneous disorders:**
*Very common:* sweating, flushing
*Uncommon:* rash, urticaria, facial oedema
*Rare:* alopecia, light sensitivity

**Endocrine disorders:**
*Unknown:* SIADH

**Nutritional and metabolic disorders:**
*Rare:* decreased appetite, weight gain or loss

**Vascular diseases:**
*Common:* orthostatic hypotension
*Uncommon:* hypertension

**General and application site disorders:**
*Common:* weakness and fatigue,
*Rare:* fever, peculiar taste, mouth or gum problems,

**Liver and bile disorders:**
*Rare:* Jaundice
*Unknown:* cholestasis

**Reproductive system and breast disorders:**
*Common:* erection disorders
*Rare:* gynaecomastia, changes in sexual performance may also rarely occur.
*Very rare:* galactorrhoea, swelling of testicles

**Psychiatric disorders:**
*Common:* confusion, decreased libido
*Uncommon:* hypomania, mania, anxiety, insomnia (especially on sudden withdrawal), changes in sleep patterns (including nightmares)
*Rare:* confusional states / delirium (especially in older patients), hallucinations (in patients with schizophrenia), irritability
Unknown Cases of suicidal ideation and suicidal behaviours have been reported during nortriptyline therapy or early treatment discontinuation (see Section 4.4). Agitation, restlessness, aggressive outbursts, delusions, orgasm disorders in women, increased libido, disorientation

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

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

4.9 OVERDOSE

Individual differences in metabolism may lead to symptoms and signs of overdose even after relatively modest excess ingestion, irrespective of age.

Signs and symptoms: 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. Early transfer to a hospital with an intensive care unit is recommended. Activated charcoal may be more effective than emesis or lavage to reduce absorption, although combination therapy may be appropriate depending on the time since ingestion.

Ventricular arrhythmias, especially when accompanied by lengthened QRS intervals, may respond to alkalinisation by hyperventilation or administration of sodium bicarbonate or the rapid infusion of hypertonic sodium chloride (100-200mmol). Serum electrolytes should be monitored and managed. Refractory arrhythmias may respond to propranolol, bretylium or lignocaine (usually 1-1.5mg/kg iv followed by 1-3mg/min). Quinidine and procainamide usually should not be used because they may exacerbate arrhythmias and conduction already slowed by the overdose.

Seizures or agitation 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. Doses as low of 50mg (especially in children) may lead to clinically significant symptoms. Cardiotoxicity and convulsions are commoner in children and toxicological advice is recommended in all cases.

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. Nortriptyline itself is a stronger inhibitor of pre-synaptic noradrenaline reuptake than of serotonin, and is less anticholinergic than amitriptyline whilst having stronger antihistaminergic effects.

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

5.2 PHARMACOKINETIC PROPERTIES

Absorption: oral administration results in maximum plasma concentrations in approximately 5 hours (Tmax = 5.5 ±1.9 hours; range 4.0-8.8 hours). The mean oral bioavailability is 51% (Fabs = 0.51±0.05; range 0.46-0.59).

Distribution: The apparent volume of distribution (Vdβ), estimated after intravenous administration is 1633 ± 268 l; range 1460 to 2030 (21 ± 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-demethyl-nortriptyline 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 ± 7.9 hours; range 16-38 hours). The mean systemic clearance ($Cl_s$) is 30.6 ± 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. Pharmacokinetic / pharmacodynamic relationship The therapeutic plasma concentration in endogenous depression is 50-140 ng/ml (~190-530 nmol/l). Levels above 170-200 ng/ml are associated with an increased risk of cardiac conduction disturbance in terms of a prolonged QRS complex or an AV block.

5.3 PRECLINICAL SAFETY DATA
Malformations have been observed in animal reproduction studies, in particular cranial malformations and encephalocele.

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 RESTATEMENT
NRIM Limited
Unit 15 Moorcroft,
Harlington Road,
Hillingdon,
UB8 3HD
UK
8 MARKETING AUTHORISATION NUMBER(S)
   PL 20620/0019

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

10 DATE OF REVISION OF THE TEXT
    10/11/2011
Module 3
Patient Information Leaflet

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. Before you take Nortriptyline Tablets
2. How to take Nortriptyline Tablets
3. Possible side effects
4. How to store Nortriptyline Tablets
5. Further Information

1. WHAT NORTRIPTYLINE TABLETS ARE AND WHAT ARE THEY USED FOR?
Nortriptyline belongs to a class of medicines called tricyclic antidepressants. Nortriptyline tablets are used:
- to treat major depression.

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 for adults only.

Do not take Nortriptyline Tablets if you:
- have had a rash or any other allergic reaction to Nortriptyline.
- have recently had a heart attack or if you have other heart problems such as palpitations or irregular heartbeats.
- are taking, or have stopped taking, within the last 14 days, a monoamine oxidase inhibitor (MAOI) e.g. phenelzine, isocarboxazid or tranylcypromine. If you are taking monoamine oxidase inhibitors you must stop this at least 24 hours before starting nortriptyline.

Take special care with Nortriptyline Tablets
Do not take Nortriptyline Tablets without first discussing your condition with your doctor or pharmacist 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 problems.
- have suffered from an allergic reaction with another tricyclic antidepressant, as cross sensitivity may occur.
- have ever had epilepsy.
- are diabetic.
- have breast feeding.
- have an enlarged prostate.
- have glaucoma or raised intra-ocular pressure.
- are agitated or suffer from schizophrenia.
- have low blood pressure or heart failure.
- have severe liver disease.
- have suffered from urinary retention.

Thoughts of suicide and worsening of your depression or manic disorder
If you are depressed and/or have anxiety disorders you can sometimes have thoughts of harming or killing yourself. These may be increased when first starting antidepressants, since these medicines all take time to work, usually about two weeks but sometimes longer.

You may be more likely to think like this:
- if you have previously had thoughts about killing or harming yourself.
- if you are young, or if you have no-one to talk to about your depression.
- if you have had 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 that you are depressed and/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 have recently been taking, any medicines known as monoamine oxidase inhibitors (MAOIs). MAOIs include phenelzine, isocarboxazid or tranylcypromine. If you are taking monoamine oxidase inhibitors you must stop this at least 24 hours before starting nortriptyline.
- are taking any medicine for your heart or for high blood pressure.
- are taking tricyclic antidepressants, including amitriptyline, imipramine, doxepin, clomipramine and maprotiline.
- are taking isocarbamoyl derivatives, such as tagamet.
- are taking any other medicines including other antidepressants or medicine for bowel complaints, breathing difficulties, bronchitis, glaucoma or prostate trouble.
- are taking levodopa or levodopa derivatives.
- are taking antifungal medicines such as fluconazole and terbinafine.
- are taking the antihistamine astemizole or terfenadine.
- are taking the pain killer tramadol.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines including medicines obtained 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.

The amount of nortriptyline in breast milk is low, and no adverse effects on breast fed infants of mothers taking nortriptyline have been reported. However, you should discuss the fact that you are breast feeding with your doctor if you are prescribed nortriptyline.

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

2. HOW TO TAKE NORTRIPTYLINE TABLETS

Always take Nortriptyline tablets exactly as your doctor has told you. If you have any questions, you should check with your doctor or pharmacist, if you are not sure.

Adults

- The usual dose an adult will start on is 25mg two to three times daily. You will usually be told to increase your dose gradually no more rapidly than by 25mg every other day until you are taking the usual maintenance dose of 75 to 100mg a day. Once you feel better, you will be told to carry on taking Nortriptyline Tablets at the same 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.
- If you are elderly you will usually be told to start on one 10mg tablet three times a day. Dose increases should also be gradual by no more than 10mg every other day. If you require a dose of 50mg or over, your doctor will arrange for you to have a recording of your heart rate and 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.

If you take more Nortriptyline Tablets than you should

Do not take more tablets than your doctor tells you to. If you ever take too many, or if a child has taken any nortriptyline, go to the nearest hospital casualty department or tell 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 your 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, headaches, nausea, irritability and sweating.

4. POSSIBLE SIDE EFFECTS

Like all medicines Nortriptyline Tablets 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 clumsiness
- Swelling of ankles and in severe cases of the face & tongue
- Alterations in brain function (including perhaps seizures)
- 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
- Flu-like symptoms including sore throat if occurring during the first 10 weeks of treatment

The following side effects have also been reported:

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, sweating, flushing, weakness, fatigue, headache, low blood pressure, tremors, decreases in libido and erectile dysfunction.

Uncommon: More than 1 but less than 10 out of 1,000 patients.
- Dizziness, changes in sleep patterns (including nightmares), numbness, nausea (feeling sick) and vomiting, problems urinating (increased or decreased), high blood pressure are all uncommon side effects.

Rarer: More than 1 but less than 10 out of 10,000 patients.
- Peculiar taste, mouth or gum problems, confusion 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. Rarely increases in libido have been reported. 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 these may be swelling & damage to liver cells. 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.

5. HOW TO STORE NORTRIPTYLINE TABLETS

- Keep out of the reach and sight 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.
- 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 you 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 active substance in your tablet is nortriptyline hydrobromide. Each tablet contains 10mg or 25mg of nortriptyline (as the hydrobromide) 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, debossed ‘NM’ on one side and ‘10’ on other side. Nortriptyline 25mg Tablets are white to off white, round, biconvex, uncoated tablets, debossed ‘NM’ on one side and ‘25’ on other side. Nortriptyline 10mg & 25mg Tablets are packed in a white HiSP luggage bag with a white polypropylene child resistant cap and tamper evident film, containing 100 tablets.

Marketing Authorisation Holder and Manufacturer
The Marketing Authorisation Holder and Manufacturer of these tablets is Nithal Limited, Unit 15 Moorcroft, Hanlington Road, Hillingdon, UB8 3HJ, United Kingdom.

This leaflet was prepared in 10/2011
Module 4
Labelling
Module 5
Scientific discussion during Mutual Recognition procedure

1 INTRODUCTION
Marketing Authorisations were granted via the National Procedure in the UK for Nortriptyline 10mg and 25mg Tablets on 1st May 2009. Based on the review of the data on quality, safety and efficacy, Germany, Italy, the Netherlands, Spain and the UK (reference member state) considered that the applications for Nortriptyline 10mg and 25mg Tablets could be approved via the Mutual Recognition Procedure. These prescription only medicines (POM) are indicated for the treatment of major depressive episodes.

These applications for Nortriptyline 10mg and 25mg Tablets were submitted according to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of Allegron 10mg and 25mg Tablets, first approved in the UK to Eli Lilly and Company Limited on 14th February 1983 (PLR 00006/5002-3). These licences then underwent a change of ownership to King Pharmaceuticals Limited on 30th March 1998 (PL 14385/0001-2).

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.

No new non-clinical studies were conducted, which is acceptable given that the products contain a widely-used, well-known active substance. No clinical studies, with the exception of the bioequivalence study, have been performed and none are required for these applications as the pharmacology of nortriptyline hydrochloride is well-established.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A satisfactory justification has been provided for the absence of a Risk Management Plan.
II. ABOUT THE PRODUCT

| Name of the products in the Reference Member State | Nortriptyline 10mg Tablets  
Nortriptyline 25mg Tablets |
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Nortriptyline hydrochloride</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Non-selective monoamine reuptake inhibitors (N06AA)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>10mg and 25mg Tablets</td>
</tr>
</tbody>
</table>
| Reference numbers for the Mutual Recognition Procedure | UK/H/4130/001/MR  
UK/H/4130/002/MR |
| Reference Member State                          | United Kingdom (UK) |
| Member States concerned                         | Germany (DE), Italy (IT), the Netherlands (NL) and Spain (ES) |
| Marketing Authorisation Number(s)               | PL 20620/0018  
PL 20620/0019 |
| Name and address of the authorisation holder     | NRIM Limited  
Unit 15 Moorcroft,  
Harrington Road,  
Hillingdon,  
UB8 3HD  
UK |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS
S. Drug substance

INN: Nortriptyline hydrochloride.

Chemical Name:

i) 3-(10,11-dihydro-5H-dibenzo[a,d][7]annulen-5-ylidene)-N-methylpropan-1-amine hydrochloride.

ii) 5-(a-methylaminopropylidene)dibenzo[a,d] cyclohepta-[1,4] diene hydrochloride.

iii) 3-(10,11-dihydro-5H-dibenzo[a,d] cyclohepten-5-ylidene)-N-methyl propylamine hydrochloride.

iv) 10,11-dihydro-5-(3-methylaminopropylidene)-5H-dibenzo[a,d]-{1,4}cycloheptene hydrochloride.

Molecular Formula: $\text{C}_{19}\text{H}_{21}\text{N.HCl}$

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.

All aspects of the manufacture of the drug substance from its starting materials are controlled by a Certificate of Suitability.

An appropriate specification with suitable test methods and limits is provided for the active substance. The methods of testing and limits for residual solvents are in compliance with the Certificate of Suitability.

The proposed retest period is in-line with the Certificate of Suitability and is satisfactory.
P. Medicinal Product

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.

With the exception of lactose monohydrate, none of the excipients contain material from animal or human origin. 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. Confirmation has been provided that the magnesium stearate contained in these products is sourced from vegetable origin.

No genetically modified organisms have been used in the preparation of these products.

Pharmaceutical development

The objective of the development programme was to produce safe, efficacious products containing nortriptyline hydrochloride that could be considered generic medicinal products of Allegron 10mg and 25mg Tablets.

The applicant has provided suitable product development information. Valid justifications for the use and amount of each excipient have been provided.

Comparative in vitro dissolution and impurity profiles have been provided for the proposed and reference products.

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 been validated and has shown satisfactory results. Process validation data on batches of each strength have been provided and are satisfactory.

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 specifications. Certificates of analysis have been provided for any working standards used.

Container-Closure System

Both strengths of the tablet are packaged in white high-density polyethylene bottles, with a white polypropylene 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 both strengths of finished product in the packaging proposed for marketing and in accordance with current guidelines. These data 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. Bioequivalence has been shown for the test and reference product.

Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labelling are pharmaceutically acceptable. The UK SmPC texts, PIL and labelling mock-ups are included in modules 2, 3 and 4 of this report.

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
The MAA forms are pharmaceutically satisfactory.

Expert report
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
The requirements for a generic medicinal product have been met with respect to qualitative and quantitative content of the drug substance and pharmaceutical form of the products. In addition, similar dissolution and impurity profiles have been provided for the proposed and reference products. Bioequivalence has been shown for the test and reference product.

It is recommended that Marketing Authorisations are granted for these applications from a quality point of view.
III.2 NON-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of nortriptyline hydrochloride are well-known. As nortriptyline hydrochloride is widely used, well-known active substance, the applicant has not provided any new non-clinical data and none are required. An overview based on literature review is therefore appropriate.

The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

An Environmental Risk Assessment has not been submitted and one is not required for applications of this type.

It is recommended that Marketing Authorisations are granted for these applications from a non-clinical point of view.
III.3 CLINICAL ASPECTS
CLINICAL PHARMACOLOGY

With the exception of the following bioequivalence study, no new pharmacokinetic or pharmacodynamic data were submitted with these applications and none were required.

Pharmacokinetics

A randomised, two-period, single-dose, cross-over study to compare the pharmacokinetics of the test product Nortriptyline 25mg Tablets versus the reference product Allegro (nortriptyline hydrochloride) 25mg Tablets (King Pharmaceuticals Limited, UK) in healthy subjects under fasted conditions.

Blood samples were taken pre- and up to 168 hours post dose. There was a washout period of 21 days between each treatment period. Pharmacokinetic parameters were measured from the plasma and statistically analysed. Nortriptyline hydrochloride has an active metabolite, 10-hydroxy nortriptyline which dominates in the blood plasma. Therefore, this was also measured.

Results for nortriptyline hydrochloride and its active metabolite, 10-hydroxy nortriptyline are presented below:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC&lt;sub&gt;0-t&lt;/sub&gt; µg/ml</th>
<th>AUC&lt;sub&gt;0-∞&lt;/sub&gt; µg/ml</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; µg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nortriptyline:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>335.588 ± 36.157</td>
<td>418.287 ± 38.099</td>
<td>10.633 ± 0.839</td>
</tr>
<tr>
<td>Reference</td>
<td>332.668 ± 33.569</td>
<td>417.940 ± 36.619</td>
<td>10.924 ± 0.807</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>100.87 (89.64-114.94)</td>
<td>100.08 (88.78-115.10)</td>
<td>96.91 (89.04-106.13)</td>
</tr>
<tr>
<td>10-hydroxy nortriptyline:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>694.840 ± 41.089</td>
<td>831.723 ± 47.765</td>
<td>19.587 ± 1.109</td>
</tr>
<tr>
<td>Reference</td>
<td>657.539 ± 35.976</td>
<td>747.247 ± 36.833</td>
<td>20.125 ± 1.237</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>105.67 (98.21-110.95)</td>
<td>111.30 (102.04-119.42)</td>
<td>97.32 (90.62-104.03)</td>
</tr>
</tbody>
</table>

*   log-transformed values

AUC<sub>0-∞</sub> area under the plasma concentration-time curve from time zero to infinity
AUC<sub>0-t</sub> area under the plasma concentration-time curve from time zero to t hours
C<sub>max</sub> maximum plasma concentration

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC<sub>0-t</sub> and C<sub>max</sub> for nortriptyline hydrochloride and its active metabolite, 10-hydroxy nortriptyline lie within acceptable limits (80-125%). Thus, bioequivalence has been shown between the test and reference products in this study.

As the product range meet all the criteria as specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 rev 1) for a biowaiver for the other strengths, the results and conclusions of the bioequivalence study on the 25mg strength can be extrapolated to Nortriptyline 10mg Tablets.
**Efficacy**
With the exception of the data submitted during the bioequivalence study, no new efficacy data were submitted with these generic applications and none were required.

**Safety**
With the exception of the data submitted during the bioequivalence study, no new safety data were submitted with these generic applications and none were required. No new or unexpected safety concerns were raised during the bioequivalence study.

**Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling**
The SmPCs, PIL and labelling are clinically satisfactory and consistent with those for the reference products.

**Clinical Overview**
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**MAA Forms**
The MAA forms are clinically satisfactory.

**Conclusions**
From a clinical point of view, it is recommended that Marketing Authorisations are granted for these applications.
IV OVERALL CONCLUSION AND BENEFIT-RISK 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.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL
Bioequivalence has been demonstrated between the applicant’s Nortriptyline 25mg Tablets the reference product Allegron 25mg Tablets. These bioequivalence results and conclusions can be extrapolated to Nortriptyline 10mg Tablets.

No new or unexpected safety concerns arise from these applications.

The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference products.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence studies support the claim that the applicant’s products and the reference products are interchangeable. Extensive clinical experience with nortriptyline hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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