SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nortriptyline 25 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 25 mg of Nortriptyline as Nortriptyline hydrochloride.

Excipient(s) with known effect: Lactose monohydrate

Each film coated tablet contains 61.710 mg lactose monohydrate

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated Tablet

Nortriptyline 25 mg Film-coated Tablets are orange coloured, circular biconvex film coated tablet debossed with “N” & “25” separated by break line on one side and plain on other side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

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.

***The 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).

Age (years)	**Weight**		**Dose (mg)**
	kg	**lb**	
6-7	20-25	44-55	10
8-11	25-35	55-77	10-20
Over 11	35-54	77-119	25-35

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 the active substance or to any of the excipients listed in section 6.1.

• 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.

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 this 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 behavior with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy in early treatment and following dose changes. Patients (an caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behavior 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 medications, 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.

Behavioral 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).

Tricyclic antidepressants, at supra-therapeutic doses can block $GABA_A$ receptors and decrease inhibitory neuronal signals resulting in seizures (lowering seizure threshold). Caution should be exercised when using these medications in patients who may be at a high risk of developing seizures or have a known diagnosis of epilepsy. If TCAs are

prescribed they should be titrated slowly and patients should be monitored for adverse events.

Tricyclic antidepressants also affect the action of acetylcholine, a brain chemical that affects muscle movement and the automatic (also known as autonomic) functions of the body, including secretions and digestion. Tricyclic antidepressants also block the effects of histamine. Neither of these actions is believed to affect depression; however, they explain some of the more troublesome side effects associated with TCAs including visual disorders (due to its effect on intraocular pressure) and urinary retention.

It has been stated that neither fluoxetine nor TCAs have been shown to cause neurobehavioral effects in children or congenital abnormalities if the child was exposed to these antidepressants in utero. With respect to TCAs, muscle spasms, tachycardia and irritability in the neonate has been reported with the use of imipramine (a TCA) during pregnancy.

It is postulated that there might be a temporary deficiency of chemicals in brain particularly norepinephrine with abrupt withdrawal of Tricyclic antidepressants. This deficiency is compounded by the fact that down-regulated receptors (a type of proteins that are targeted by norepinephrine) will remain in their relatively hypoactive state for days to weeks. This effect is believed to result in antidepressant discontinuation syndrome directly or indirectly via downstream effects on other neurotransmitter systems (e.g., norepinephrine, dopamine, and γ-amino-butyric acid) implicated in depressive disorders.

The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsoprtion should not take this medicine.

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 (4-16 days for norfluoxetine).In a comparison study of fluoxetine (SSRI) and nortriptyline in the treatment of moderate to severe major depression, the results suggested nortriptyline was more effective than fluoxetine in the treatment of moderate to severe depression.

Concomitant therapy with other drugs that are metabolised by this isoenzyme, including other antidepressants, phenothiazines, carbamazepine, propafenone, flecainide and encainide, or that inhibit this enzyme (eg, quinidine), should be approached with caution.

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

Cardiovascular side-effects are of particular concern in children because of the efficiency with which they convert TCAs to potentially toxic 2-hydroxy metabolites.

Of the greatest concerns are the reports of sudden cardiac deaths in children on TCAs.

Though mechanism related to sudden cardiac death is not known, but changes in ECG have been reported.

Combining TCAs and MAOIs could result in enhanced monoamine transmission by an additive effect. Combination of TCAs with MAOIs was not advised owing to severe adverse reactions and fatalities. The most serious adverse reaction is serotonin syndrome, which

usually occurs very rapidly. It is suggested that TCAs with weaker serotonergic properties might be safer with respect to serotonin toxicity. The side effects are due to the synergism of the two drugs include orthostatic hypotension, dizziness, headache, urinary retention, weight gain and nausea, all of which can be caused by either drug alone.

The TCAs are thought to affect depression by inhibiting synaptic reuptake of norepinephrine and serotonin. Given chronically, these drugs decrease stores of noradrenergic catecholamines. They can cause changes on the ECG (changes in the T wave, widening of the QRS complex and prolongation of QT interval, bundle branch block or other conduction abnormalities, or PVCs). Ventricular arrhythmias and refractory hypotension may occur in higher doses. Chronic therapy with tricyclic antidepressant drugs depletes cardiac catecholamines, potentiating the cardiac depressant effects of anaesthetic agents. During anaesthesia and surgery, it is important to avoid stimulating the sympathetic nervous system.

It is postulated that there might be a temporary deficiency of synaptic monoamines particularly norepinephrine with abrupt withdrawal of TCAs. This deficiency is compounded by the fact that down-regulated receptors will remain in their relatively hypoactive state for days to weeks. This effect is believed to result in antidepressant discontinuation syndrome directly or indirectly via downstream effects on other neurotransmitter systems (e.g., norepinephrine, dopamine, and γ-amino-butyric acid) implicated in depressive disorders.

Tricyclic antidepressants also affect the action of acetylcholine, a brain chemical that affects muscle movement and the automatic (also known as autonomic) functions of the body, including secretions and digestion. Tricyclic antidepressants also block the effects of histamine. Neither of these actions is believed to affect depression; however, they explain some of the more troublesome side effects associated with Tricyclic antidepressants including visual disorders (due to its effect on intraocular pressure) and urinary retention.

Nortriptyline plasma concentration can be increased by valproic acid. Clinical monitoring is therefore recommended.

4.6 Fertility, pregnancy and lactation

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 child bearing age unless the potential benefits clearly outweigh any potential risk.

Breast-feeding:

See section 4.3.

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.

Frequency categories are defined according to the following convention:

Very common (≥1/10)

Common (≥1/100 to <1/10)

Uncommon (≥1/1,000 to <1/100)

Rare (≥1/10,000 to <1/1,000)

Very rare (<1/10,000)

Not known (cannot be estimated from the available data)

Cardiovascular: Hypotension, hypertension, palpitation, myocardial infarction, heart block, stroke, tachycardia and arrhythmias have been reported as very common (affects more than 10 per 100 users.

Psychiatric: Confusional states (especially in the elderly) with hallucinations (seeing or hearing things) are rare (affects 1-10 per 10,000 users) side-effects, disorientation, delusions; anxiety, restlessness, agitation; insomnia, panic, nightmares; hypomania; exacerbation of psychosis. Cases of suicidal ideation and suicidal behaviors have been reported during nortriptyline therapy or early treatment discontinuation (see Section 4.4). Alterations in brain functions have been reported as very rare (affects 1-10 per 100,000 users).

Neurological: Numbness, tingling, paraesthesia of extremities; inco-ordination, ataxia, tremors; peripheral neuropathy; extra pyramidal symptoms; seizures, alteration of EEG patterns; tinnitus.

Anticholinergic: Dry mouth and, rarely, associated sublingual adenitis or gingivitis; blurred vision, disturbance of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract.

Allergic: Rash, petechiae, urticaria, itching, photo sensitisation (avoid excessive exposure to sunlight); oedema (general or of face and tongue), drug fever, cross sensitivity with other tricyclic drugs.

Haematological: Bone-marrow depression, including a granulocytosis; a plastic anaemia; eosinophilia; purpura; thrombocytopenia.

Gastro-intestinal: Nausea and vomiting, anorexia, epigastric distress, diarrhoea; peculiar taste, stomatitis, abdominal cramps, black tongue, constipationis a very common (affects more than 10 per 100 users) side-effect associated with the use of TCAs, paralytic ileus.

Endocrine: Gynaecomastia in the male; breast enlargement and galactorrhoea in the female; increased or decreased libido, impotence; testicular swelling; elevation or depression of blood sugar levels are very rare (affects 1-10 per 100,000 users); syndrome of inappropriate secretion of antidiuretic hormone.

Other: Jaundice (simulating obstructive); altered liver function, hepatitis and liver Necrosis are very rare (affects 1-10 per 100,000 users) side-effects related to the use of the TCAs; weight gain or loss; sweating; flushing; urinary frequency, nocturia; drowsiness, dizziness, weakness, fatigue; headache; parotid swelling; alopecia. Blurred vision is a very common (affects more than 10 per 100 users).

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

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

Pharmacotherapeutic group: Antidepressants, ATC code: N06AA10

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

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

There are no preclinical data of relevance to the prescriber, which are additional to those already included in other sections of the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Microcrystalline cellulose,

Lactose monohydrate,

Maize starch,

Silica, colloidal anhydrous (E551),

Magnesium stearate (E572)

Coating:

Isopropyl alcohol,

Dichloromethane,

Instamoistshield A21E21116 (Orange) which contains

Hypromellose (E464),

Diethyl phthalate,

Ethyl cellulose,

Talc (E553b),

Titanium dioxide (E171),

Lake quinoline yellow (E104),

Lake erythrosine (E127)

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

36 months

HDPE containers: Discard 100 days after first opening the container.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium-PVC/PVDC clear transparent blister packs of 10, 30 and 100 tablets.

White Opaque HDPE container with white polypropylene child resistant cap available in pack size: 100 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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Ist floor, Kirkland House,

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8 MARKETING AUTHORISATION NUMBER(S)

PL 43461/0015

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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