SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Nortriptyline 10 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Nortriptyline 10 mg film-coated tablets:
Each film coated tablet contains nortriptyline hydrochloride equivalent to 10 mg of nortriptyline.
Excipients with known effect:
Nortriptyline 10 mg film-coated tablets contain lactose monohydrate.

3 PHARMACEUTICAL FORM
Film-coated tablet
Nortriptyline 10 mg film-coated tablets:
Nortriptyline 10 mg film-coated tablets are white to off coloured, round biconvex, debossed with ‘N’ on the one side and 10 on the other side.

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
Posology:
Adults: The usual adult dose is 25 mg 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 100 mg daily are administered, plasma levels of Nortriptyline should be monitored and maintained in the optimum range of 50 to 150ng/ml. Doses above 150 mg 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 50 mg/day in divided doses.

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

**Plasma levels:** Optimal responses to nortriptyline have been associated with plasma concentrations of 50 to 150 ng/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 percent 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).

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<tr>
<th>Age (Years)</th>
<th>Weight</th>
<th>Dose (mg)</th>
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<td>kg</td>
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<td>6-7</td>
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<td>&gt;11</td>
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<td>77-119</td>
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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.
Method of administration:
Oral use

4.3 Contraindications

- Hypersensitivity to nortriptyline
- Recent myocardial infarction, any degree of heart block or other cardiac arrhythmias
- Severe liver disease
- Mania
- Nortriptyline is contra-indicated for the nursing mother and for children under the age of six years

Please also refer to Section 4.5 (Interaction with other medicinal products and other forms of interaction).

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 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 in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Withdrawal symptoms, including insomnia, irritability and excessive perspiration, may occur on abrupt cessation of therapy.

The use of nortriptyline in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms. If administered to
overactive or agitated patients, increased anxiety and agitation may occur. In manic depressive patients, nortriptyline may cause symptoms of the manic phase to emerge.

Cross sensitivity between nortriptyline and other tricyclic antidepressants is a possibility.

Patients with cardiovascular disease should be given nortriptyline only under close supervision because of the tendency of the drug to produce sinus tachycardia and to prolong the conduction time. Myocardial infarction, arrhythmia and strokes have occurred. Great care is necessary if nortriptyline is administered to hyperthyroid patients or to those receiving thyroid 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.

Behavioural changes may occur in children receiving therapy for nocturnal enuresis. If possible, the use of nortriptyline should be avoided in patients with narrow angle glaucoma or symptoms suggestive of prostatic hypertrophy.

The possibility of a suicide attempt by a depressed patient remains after the initiation of treatment. This possibility should be considered in relation to the quantity of drug dispensed at any one time.

When it is essential, nortriptyline may be administered with electroconvulsive therapy, although the hazards may be increased.

Both elevation and lowering of blood sugar levels have been reported. Significant hypoglycaemia was reported in a Type II diabetic patient maintained on chlorpropamide (250 mg/day), after the addition of nortriptyline (125 mg/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 the brain particularly norepinephrine with abrupt withdrawal of Tricyclic antidepressants. This deficiency is compounded by the fact that down-regulated receptors (types of protein
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-aminobutyric acid) implicated in depressive disorders.

Excipient with known effect:
Nortriptyline 10 mg and 25 mg film-coated tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. Nortriptyline 25 mg film-coated tablets also contain sunset yellow (E110) which may cause allergic reactions.

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 cytochrome P450IID6 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 the mechanism related to sudden cardiac death is not known, 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 chemicals in the brain particularly norepinephrine with abrupt withdrawal of Tricyclic antidepressants. This deficiency is compounded by the fact that down-regulated receptors (types of protein 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-aminobutyric acid) implicated in depressive disorders.

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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 childbearing age unless the potential benefits clearly outweigh any potential risk.

**Breast-feeding:**

There is very little information about the safety of using most tricyclic antidepressants (nortriptyline like drugs) while breastfeeding. The risk to the fetus is low, although the full risks are not known. If the doctor recommends taking a tricyclic antidepressant while breastfeeding, the patient should watch for excessive tiredness, decreased feeding, and weight loss in the baby. These may be signs that the baby is getting too much of the tricyclic antidepressant, and the doctor may need to decrease the dose or recommend a different depression medication. The doctor may also advise to stop breastfeeding, especially in the case of severe symptoms in the baby.

**Fertility:**

No human data on the effect of nortriptyline on fertility are available.

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.

**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) disorientation, delusions; anxiety, restlessness, agitation; insomnia, panic, nightmares; hypomania; exacerbation of psychosis. Cases of suicidal ideation and suicidal behaviours 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; extrapyramidal symptoms; seizures, alteration of EEG patterns; tinnitus.
Anticholinergic: Dry mouth and, rarely, associated sublingual adenitis or gingivitis; blurred vision, disturbance of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract.

Allergic: Rash, petechiae, urticaria, itching, photosensitisation (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 agranulocytosis; aplastic anaemia; eosinophilia; purpura; thrombocytopenia.

Gastro-intestinal: Nausea and vomiting, anorexia, epigastric distress, diarrhoea; peculiar taste, stomatitis, abdominal cramps, black tongue, constipation (very common side effect associated with the use of TCAs affects more than 10 per 100 users), 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 (very rare side effect 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 (very rare side-effects related to the use of the TCAs affects 1-10 per 100,000 users); weight gain or loss; sweating; flushing; urinary frequency, nocturia; drowsiness, dizziness, weakness, fatigue; headache; parotid swelling; alopecia. Blurred vision (very common side effect 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 SSRIs 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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose
Signs and symptoms:
50 mg 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 100 msec 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 procaainamide 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 those of Amitriptyline. It is the principal active metabolite of Amitriptyline.

In the treatment of depression, nortriptyline is given by mouth as the hydrochloride in doses equivalent to nortriptyline 10 mg 3 or 4 times daily initially, gradually increased to 25 mg 4 times daily as necessary. A suggested initial dose for adolescents and the elderly is 10 mg 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose Monohydrate
Anhydrous Calcium Hydrogen Phosphate
Maize Starch
Magnesium Stearate
Hypermellose
Macrogol (PEG 6000)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years
HDPE container: 100 tablets
Unopened: 3 years
After opening: within 60 days

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.
6.5 Nature and contents of container
Each Aluminium/clear PVC blister contains 10 tablets.
Blister pack sizes: 10 tablets, 30 tablets and 100 tablets.
HDPE container with polypropylene screw on cap pack size: 100 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
Key Pharmaceuticals Ltd.
Galen House, 83 High Street
Somersham, Cambridgeshire
PE28 3JB, UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 34424/0026

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
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10 DATE OF REVISION OF THE TEXT
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