SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nortriptyline 25 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Nortriptyline 25 mg Capsules:

Each capsule contains Nortriptyline Hydrochloride EP equivalent to 25mg nortriptyline base.

Excipient(s) with known effect Lactose

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard.

Hard gelatin capsules with a white, opaque body, yellow opaque cap and a hard gelatin capsule with white to off-white powder fill. The capsules are imprinted with "APO 25".

4.1 Therapeutic indications

Nortriptyline is indicated for the treatment of Major Depressive Episodes in adults.

4.2 Posology and method of administration

Posology

Adults: The usual adult dose is 25mg three or four times daily. Dosage should begin at a lowlevel 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 underclose supervision. The physician should initiate dosage at a low level and increase it gradually, noting carefully the clinical response and any evidence of intolerance. Following remission, maintenance medication may be required for a longer period of time at the lowest dose that will maintain remission.

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

Elderly: 30 to 50 mg/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. 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 asprimary determinants of dosage changes.

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 shouldconsult the laboratory professional staff.

Cytochrome P450 isoenzyme CYP2D6 and poor metabolisers
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. Thepercentage of ‘poor metabolisers’ in a population is also affected by its ethnic origin.

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.

Paediatric population: Nortriptyline should not be used in children and adolescents aged less than 18 years, as safety and efficacy have not been established (see section
4.4).

Method of administration

For oral administration.

4.3 Contraindications

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

Concomitant treatment with MAOIs (monoamine oxidase inhibitors) is contraindicated.

Recent myocardial infarction, any degree of heart block or other cardiac arrhythmias and coronary artery insufficiency.

Severe liver disease.

Mania.

Nortriptyline is contraindicated for the nursing mother and for children under the age of sixyears (see section 4.5).

Simultaneous administration of nortriptyline and MAOIs may cause serotonin syndrome (a combination of symptoms, possibly including agitation, confusion,tremor, myoclonus and hyperthermia).

Treatment with nortriptyline may be instituted 14 days after discontinuation of irreversible non-selective MAOIs and minimum one day after discontinuation of thereversible moclobemide. Treatment with MAOIs may be introduced 14 days after discontinuation of nortriptyline.

4.4 Special warnings and precautions for use

Paediatric population
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, selfharm 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 improvementmay 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 suicidalthoughts 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 onabrupt cessation of therapy.

The use of nortriptyline in schizophrenic patients may result in an exacerbation of the psychosisor 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. Arrhythmia 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 arrhythmias and hypotension. Great care is necessary if nortriptyline is administered to hyperthyroid patients or to those receiving thyroid medication, since cardiac arrhythmias may develop.

Cardiac arrhythmias and severe hypotension are likely to occur with high dosage. They may alsooccur in patients with pre-existing heart disease taking normal dosage.

QT interval prolongation
Cases of QT interval prolongation and arrhythmia have been reported during the post-marketing period. Caution is advised in patients with significant bradycardia, in patients with uncompensated heart failure, or in patients concurrently taking QT-prolonging drugs. Electrolytedisturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) are known to be conditions increasing the proarrythmic risk.

Anaesthetics given during tri/tetracyclic antidepressant therapy may increase the risk of arrhythmias and hypotension. If possible, discontinue this medicinal product several days beforesurgery; if emergency surgery is unavoidable, the anaesthetist should be informed that the patient is being so treated.

Great care is necessary if amitriptyline is administered to hyperthyroid patients or to thosereceiving thyroid medication, since cardiac arrhythmias may develop.

Elderly patients are particularly susceptible to orthostatic hypotension.

This medical product should be used with caution in patients with convulsive disorders, urinaryretention, prostatic hypertrophy, hyperthyroidism, paranoid symptomatology and advanced hepatic or cardiovascular disease, pylorus stenosis and paralytic ileus.

In patients with the rare condition of shallow anterior chamber and narrow chamber angle,attacks of acute glaucoma due to dilation of the pupil may be provoked.

In manic-depressives, a shift towards the manic phase may occur; should the patient enter amanic phase amitriptyline should be discontinued.

As described for other psychotropics, amitriptyline may modify insulin and glucose responses calling for adjustment of the antidiabetic therapy in diabetic

patients; in addition the depressiveillness itself may affect patients' glucose balance.

Hyperpyrexia has been reported with tricyclic antidepressants when administered withanticholinergic or with neuroleptic medications, especially in hot weather.

Amitriptyline should be used with caution in patients receiving SSRIs (see sections 4.2 and 4.5).

Serotonin syndrome
Concomitant administration of Nortriptyline and buprenorphine containing medicinal products (e.g. includes buprenorphine/naloxone) may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5).

If concomitant treatment with buprenorphine containing medicinal products (e.g. includes buprenorphine/naloxone) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

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.

Cardiac arrythmias are likely to occur with high dosage. They may also occur in patients with preexisting heart disease taking normal dosage.

Unmasking of Brugada syndrome has been reported in patients treated with nortriptyline. Brugada syndrome is a rare hereditary disease of the cardiac sodium channel with characteristic ECG changes (ST segment elevation and T wave abnormalities in the right precordial leads), which may lead to cardiac arrest and/or sudden death. Nortriptyline should generally be avoided in patients with Brugada syndrome or those suspected of having Brugada syndrome. Caution is advised in patient with risk factors such as a family history of cardiac arrest or sudden death (see sections 4.8 and 4.9).

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.

Paediatric population
Long-term safety data in children and adolescents concerning growth, maturation and cognitiveand behavioural development are not available (see section 4.2).

Excipients
The pellets in the capsule contain lactose.
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency orglucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Potential for amitriptyline to affect other medicinal products

MAOIs (non-selective as well as selective A (moclobemide) and B (selegiline)) - risk of "serotonin syndrome" (see section 4.3). 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 be used cautiously when co-administered with buprenorphine containing medicinal products (e.g., includes buprenorphine/naloxone), as the risk of serotonin syndrome; a potentially life-threatening condition, is increased (see section 4.4).

Sympathomimetic agents: Amitriptyline may potentiate the cardiovascular effects of adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine, and

phenylpropanolamine (e.g. as contained in local and general anaesthetics and nasal decongestants).

Adrenergic neurone blockers: Tricyclic antidepressants may counteract the antihypertensive effects of centrally acting antihypertensives such as guanethidine, debrisoquine, betanidine, clonidine and methyldopa. Concurrent administration of reserpine has been shown to produce a 'stimulating' effect in some depressed patients. It is advisable to review all antihypertensive therapy during treatmentwith tricyclic antidepressants.

Anticholinergic agents: Tricyclic antidepressants may potentiate the effects of these drugs on the eye, central nervous system, bowel and bladder; concomitant use of these should be avoided due to an increased risk of paralytic ileus, hyperpyrexia, etc. 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.

Drugs which prolong the QT-interval including antiarrhythmics such as quinidine, the antihistamines astemizole and terfenadine, some antipsychotics (notably pimozide and sertindole), cisapride, halofantrine, and sotalol, may increase the likelihood of ventricular arrhythmias when taken with tricyclic antidepressants. 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.

Use caution when using amitriptyline and methadone concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects.
Caution is also advised for co-administration of amitriptyline and diuretics inducinghypokalaemia (e.g. furosemide)

Thioridazine: Co-administration of amitriptyline and thioridazine (CYP2D6 substrate) should be avoided due to inhibition of thioridazine metabolism and consequently increased risk of cardiac side effects

Tramadol: Concomitant use of tramadol (a CYP2D6 substrate) and tricyclic antidepressants (TCAs), such as amitriptyline increases the risk for seizures and serotonin syndrome.
Additionally, this combination can inhibit the metabolism of tramadol to the active metabolite and thereby increasing tramadol concentrations potentially causing opioid toxicity.

Antifungals such as fluconazole and terbinafine increase serum concentrations of tricyclics and accompanying toxicity. Syncope and torsade de pointes have occurred.

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.

CNS depressants: Tricyclic antidepressants may potentiate the CNS depressant effect of alcohol. Barbiturates may increase the rate of metabolism of nortriptyline.

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.

Tricyclic antidepressants (TCA) including amitriptyline are primarily metabolised by the hepatic cytochrome P450 isozymes CYP2D6 and CYP2C19, which are polymorphic in the population. Other isozymes involved in the metabolism of amitriptyline are CYP3A4, CYP1A2 and CYP2C9.

CYP2D6 inhibitors: The CYP2D6 isozyme can be inhibited by a variety of drugs, e.g. neuroleptics, serotonin reuptake inhibitors, beta blockers, and antiarrhythmics. Examples of strong CYP2D6 inhibitors include bupropion, fluoxetine, paroxetine and quinidine. These drugs may produce substantial decreases in TCA metabolism and marked increases in plasma concentrations. Consider to monitor TCA plasma levels, whenever a TCA is to be co-administered with another drug known to be an inhibitor of CYP2D6. Dose adjustment of amitriptyline may be necessary (see section 4.2).

Other Cytochrome P450 inhibitors: Cimetidine, methylphenidate and calcium-channel blockers (e.g. diltiazem and verapamil) may increase plasma levels of tricyclic antidepressants and accompanying toxicity. A decrease may occur when cimetidine therapy is discontinued. Antifungals such as fluconazole (CYP2C9 inhibitor) and terbinafine (CYP2D6 inhibitor) have been observed to increase serum levels of amitriptyline and nortriptyline.

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).

Nortriptyline plasma concentration can be increased by valproic acid. Clinical

monitoring is therefore recommended. 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.

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.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Nortriptyline is the principal active metabolite of amitriptyline. For amitriptyline only limitedclinical data are available regarding exposed pregnancies.

Animal studies have shown reproductive toxicity (see section 5.3).

Amitriptyline is not recommended during pregnancy unless clearly necessary and only aftercareful consideration of the risk/benefit.

During chronic use and after administration in the final weeks of pregnancy, neonatal withdrawal symptoms can occur. This may include irritability, hypertonia, tremor, irregularbreathing, poor drinking and loud crying and possibly anticholinergic symptoms (urinary retention, constipation).

Breast-feeding

Nortriptyline is the principal active metabolite of amitriptyline. Amitriptyline and its metabolitesare excreted into breast milk (corresponding to 0.6 % - 1 % of the maternal dose). A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast- feeding or to discontinue/abstain from the therapy of this medicinal product taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

The reproductive toxicity of nortriptyline has not been investigated in animals.

For its parent substance amitriptyline, association with an effect on fertility in rats, namely a reduced pregnancy rate was observed (see section 5.3).

4.7 Effects on ability to drive and use machines

Nortriptyline has moderate influence on the 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. Some of the below mentioned side effects e.g. headache, tremor, disturbance in attention, constipation and decreased libido may also be symptoms of depression and usually attenuate when the depressivestate improves.

In the listing below the following convention is used: MedDRA system organ class / preferred term;
Very common ($\geq$ 1/10); Common ($\geq$ 1/100, < 1/10);
Uncommon ($\geq$ 1/1,000, < 1/100);
Rare ($\geq$ 1/10,000, < 1/1,000);
Very rare (<1/10,000);
Not known (cannot be estimated from the available data).

MedDRA SOC	Frequency	Preferred Term
Blood and lymphatic system disorders	Rare	Bone marrow depression, agranulocytosis, leucopenia, eosinophilia, thrombocytopenia.
	Not known	Aplastic anaemia, purpura
Endocrine Disorders	Not known	Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
Metabolism and nutritiondisorders	Rare	Decreased appetite
	Not Known	Changes of blood sugar levels Hyponatraemia
Psychiatric disorders	Very common	Aggression.
	Common	Confusional state (especially in the elderly) with hallucinations, libido decreased,agitation.
	Uncommon	Hypomania, mania, anxiety, insomnia,nightmare
	Rare	Delirium (in elderly patients), hallucination (in schizophrenic patients)
	Not Known	*Suicidal ideation and suicidal behavior. Paranoia, panic, delusions, disorientation,

		restlessness, hypomania, exacerbation of psychosis.
Nervous system disorders	Very common	Tremor, dizziness, headache
	Common	Disturbance in attention, dysgeusia. paresthesia, ataxia.
	Uncommon	Convulsion.
	Rare	Akathisia, dyskinesia.
	Not known	Extrapyramidal disorder, numbness, tingling, incoordination, ataxia, peripheral neuropathy, seizures, alteration of EEG patterns, drowsiness, dizziness
Eye disorders	Very common	Accommodation disorder, blurred vision.
	Common	Mydriasis.
	Very rare	Acute glaucoma.
Ear and labyrinth disorders	Uncommon	Tinnitus.
Cardiac disorders	Very common	Palpitations, tachycardia.
	Common	Atrioventricular block, bundle branchblock,
	Uncommon	Collapse conditions, worsening of cardiac failure.
	Rare	Arrhythmia.
	Very rare	Cardiomyopathies, torsades de pointes.
	Not known	Hypotension, stroke, myocardial infarction, Hypersensitivity myocarditis, Brugada Syndrome (unmasking)
Vascular disorders	Common	Orthostatic hypotension.
	Uncommon	Hypertension.
	Not known	Hyperthermia.
Respiratory, thoracic, and mediastinal disorders	Very common	Congested nose.
	Very rare	Allergic inflammation of the pulmonary alveoli and of the lung tissue, respectively (alveolitis, Löffler's syndrome).
Gastrointestinal disorders	Very common	Dry mouth and, rarely, associated sublingual adenitis or gingivitis; constipation, nausea.
	Uncommon	Diarrhoea, vomiting, tongue oedema, epigastric distress, peculiar taste, stomatitis, abdominal cramps, black tongue.

	Rare	Salivary gland enlargement, ileus paralytic.
	Not known	Anorexia
Hepatobiliary disorders	Uncommon	Hepatic impairment (e.g. cholestaticliver disease).
	Rare	Jaundice.
	Not known	Hepatitis, liver necrosis
Skin and subcutaneous tissue disorders	Very common	Hyperhidrosis.
	Uncommon	Rash, urticaria, face oedema.
	Rare	Alopecia, photosensitivity reaction.
	Not known	Petechiae, itching, flushing
Renal and urinary disorders	Common	Micturition disorders.
	Uncommon	Urinary retention.
	Not known	Dilation of the urinary tract, nocturia
Reproductive system and breast disorders	Common	Erectile dysfunction.
	Uncommon	Breast enlargement, testicular swelling, Galactorrhoea.
	Rare	Gynaecomastia.
	Not known	Impotence; testicular swelling
General disorders and administration site conditions	Common	Fatigue, feeling thirst.
	Rare	Pyrexia.
	Not known	Weakness, drug fever, cross sensitivity with other tricyclic drugs
Investigations	Very common	Weight increased.
	Common	Electrocardiogram abnormal, electrocardiogram QT prolonged, electrocardiogram QRS complex prolonged, hyponatremia.
	Uncommon	Intraocular pressure increased.
	Rare	Weight decreased. Liver function test abnormal, blood alkaline phosphatase increased, transaminases increased.

*Cases of suicidal ideation and suicidal behaviours have been reported during nortriptylinetherapy or early after treatment discontinuation (See section 4.4).

Withdrawal Symptoms:

Abrupt cessation of treatment after prolonged therapy may produce nausea, headache andmalaise.

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 leadingto this risk is unknown.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continues 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; website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the **Google Play** or **Apple App Store**.

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 l00msec 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.

Brugada syndrome (unmasking) and Brugada ECG pattern (BEP) have been reported in post-marketing surveillance in association with nortriptyline overdose.

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. 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 cardiacrhythm 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 as 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.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidepressants, ATC code: N06AA10

Nortriptyline is a tricyclic antidepressant with actions and uses similar to those ofAmitriplyline. 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 the elderly is 10mg thrice daily. Inappropriately high plasma concentrations of Nortriptyline have been associatedwith deterioration in antidepressant response. Since Nortriptyline has prolonged half-life, once daily dosage regimens are also suitable, usually given at night.

Paediatric population: Available trial data from small randomised controlled trials in major depressive disorder do not support use in children. Efficacy and safety have not been demonstrated.

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)ß, 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 demethylnortriptyline is also formed to some extent. The metabolites have the same profile as nortiptyline 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 ß) 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

Nortriptyline is the principal active metabolite of amitriptyline. Amitriptyline inhibited ion channels, which are responsible for cardiac repolarization (hERG channels), in the upper micromolar range of therapeutic plasma concentrations. Therefore, amitriptyline may increase the risk for cardiac arrhythmia (see section 4.4).

The genotoxic potential of amitriptyline has been investigated in various *in vitro* and *in vivo* studies. Although these investigations revealed partially contradictory results, particularly a potential to induce chromosome aberrations cannot be excluded. Long-term carcinogenicity studies have not been performed.

In reproductive studies teratogenic effects were not observed in mice, rats, or rabbits when amitriptyline was given orally at doses of 2-40 mg/kg/day (up to 13 times the maximum recommended human amitriptyline dose of 150 mg/day or 3 mg/kg/day for a 50-kg patient). However, literature data suggested a risk for malformations and delays in ossification of mice, hamsters, rats and rabbits at 9 33 times the maximum recommended dose. There was a possible association with an effect on fertility in rats, namely a lower pregnancy rate. The reason for the effect on fertility is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Stearic Acid,

Lactose Monohydrate,

Maize Starch

Talc

Capsule shell:

White/Yellow shell:

Titanium dioxide (E171)

Yellow iron oxide(E172)

Gelatin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

Do not use this medicine after the expiry date which is stated on blister or carton after EXP. That expiry date refers to the last day of that month

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

High density polyethylene bottles closed with polypropylene caps containing 100 capsules.

Aluminium/aluminium blister strips containing 100 capsules.

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

Kent Pharmaceuticals
Limited,
2nd Floor,
Connect 38,
1 Dover Place,
Ashford,
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England,
TN23 1FB.

8 MARKETING AUTHORISATION NUMBER(S)

PL 08215/0110

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08/10/2019

10 DATE OF REVISION OF THE TEXT

20/01/2026