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

Excipient with known effect

Each tablet contains 43.06mg of lactose monohydrate.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet
White to off-white round biconvex tablets, debossed 'NO' on one side and '10' on the other side.

4 CLINICAL PARTICULARS

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 low level (50mg once daily or 25mg 2-3 times daily). If necessary, dose could be gradually increased in 25mg increments no more 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.

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).

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

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
- Recent myocardial infarction, any degree of heart block or other cardiac arrhythmias
- Severe liver disease
- Mania
- Nortriptyline is contraindicated for the nursing mother.

Please also refer to section 4.5.

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, 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 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.

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).

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.

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.

Excipients
The tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Drug interactions:
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).

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 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).

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 (e.g. quinidine), should be approached with caution.

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.

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, halofrantine, and sotalolcan increase the risk for ventricular arrhythmias 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 verampanil) 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.

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:
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.

Cardiovascular: Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke, Brugada syndrome (unmasking).

Psychiatric: Confusional states (especially in the elderly) with hallucinations, 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).

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, 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; syndrome of inappropriate secretion of antidiuretic hormone.

Metabolism and nutrition disorders: Hyponatraemia.

Other: Jaundice (simulating obstructive); altered liver function, hepatitis and liver necrosis; weight gain or loss; sweating; flushing; urinary frequency, nocturia; drowsiness, dizziness, weakness, fatigue; headache; parotid swelling; alopecia.

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 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

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. 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 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 Amitriplyline. It is the principal active metabolite of Amitriplyline. 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.

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

<u>Absorption:</u>

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

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 AUTHORISATION HOLDER

Accord-UK Ltd
(Trading style: Accord)
Whiddon Valley
Barnstaple
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EX32 8NS

8 MARKETING AUTHORISATION NUMBER(S)

PL 00142/0953

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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