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 nortriptyline (as hydrochloride).

Excipient with known effect: Each tablet contains 75 mg of lactose monohydrate and 0.04 mg of sunset yellow FCF (E110).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Orange colored, round, biconvex, film-coated tablets debossed with ‘N’ and ‘T’ on either side of breakline on one face and other face plain with an approximate diameter of 8.10 mm.

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 treatment of Major Depressive Episodes in adults.

4.2 Posology and method of administration

Posology

The dosage should be started at a low level and increased gradually, in which the clinical effect and any signs of intolerance must be monitored closely. Dosages higher than 150 mg/day are preferably limited to hospitalised patients (up to 200-250 mg). The optimum therapeutic plasma level of nortriptyline is between 50 – 150 ng/ml.

Adults

The usual adult dose is 25 mg three or four times daily. The dose should be started at a low level and gradually increased. 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 150 ng/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 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 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.

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.

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.

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 CYP2D6. 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.

Paediatric patients

The use of Nortriptyline in children and adolescents is not recommended on account of the lack of data about the safety and efficacy (see section 4.4).

Reduced kidney function

Renal failure does not affect kinetics of nortriptyline. This medicinal product can be given in usual doses to patients with renal failure.

Reduced liver function

Careful dosing and, if possible, plasma level determination are recommended, the optimum levels are between 50-150 ng/ml.

Period of treatment

The antidepressant effect generally starts after 2 to 4 weeks. Treatment with antidepressants is symptomatic and must be continued for a considerable time, generally up to 6 months after recovery to prevent a relapse.

Stopping

If the treatment is stopped, the agent must be withdrawn gradually over a number of weeks.

Method of administration

For oral administration.
The tablets are taken with water.

4.3 Contraindications

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

Recent myocardial infarction. Any form of heart block, cardiac arrhythmias or coronary insufficiency.

As with other tricyclic antidepressants, nortriptyline should not be prescribed to patients who are treated with monoamine-oxidase inhibitors (MAOIs), see section 4.5. Concomitant use of nortriptyline and a MAOI can lead to the serotonin syndrome (a combination of symptoms which can include: agitation, confusion, tremor, myoclonia and hyperthermia). Nortriptyline therapy can start 14 days after stopping an irreversible non-selective MAOI, and, at a minimum, 1 day after stopping the reversible MAOI moclobemide. Treatment with MAOIs can start 14 days after stopping nortriptyline (see section 4.5).

4.4 Special warnings and precautions for use

Suicide/suicidal thoughts or worsening of the condition

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 it is possible that improvement may not occur during the first few weeks or more, patients should be closely monitored until such an 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 patients exhibiting a significant degree of suicidal thoughts before the beginning of the treatment, are known to be at greater risk of developing suicidal thoughts or committing suicide attempts and these patients should always be very closely monitored during the treatment. A meta-analysis of placebo-controlled clinical trials into antidepressants in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with the use of antidepressants compared with placebo in patients less than 25 years old.

Patients, in particular high-risk patients, should be monitored closely during treatment with these medicines, in particular at the beginning of treatment and after dosage adjustments. Patients (and caregivers of patients) must be made aware of the need to look out for any clinical worsening, suicidal behaviour or suicidal thoughts and unusual changes in behaviour and the need to seek medical advice immediately if these symptoms occur.

In connection with the risk of suicide, particularly at the beginning of the treatment, only a limited quantity should be given to the patient.

Paediatric population

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. Suicide-related behaviours (suicide attempts and thoughts about suicide) and hostility (mainly aggression, opposition behaviour and anger) were seen more commonly in children and adolescents treated with antidepressants versus those treated with placebo. 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.

Other special warnings and precautions for use

Nortriptyline should not be used in combination with a MAOI (see sections 4.3 and 4.5).

On treatment with a high dose, arrhythmias of the heart and severe hypotension can occur. Patients should be monitored for arrhythmias on treatment with high doses. Arrhythmias and severe hypotension can also occur in patients with existing heart conditions who are treated with a normal dose.

Nortriptyline should be used with caution in patients with convulsions, micturition disorders/urinary retention, pyloric stenosis or paralytic ileus, prostate hypertrophy, hyperthyroidism, paranoid symptoms and an advanced liver or cardiovascular disease. Caution with dosing is also recommended in patients with low blood pressure.

Caution is recommended in connection with the risk of cardiac arrhythmias on the administration of nortriptyline to patients with hyperthyroidism or who are receiving thyroid medication.

In patients with a rare eye condition such as a shallow anterior chamber or a narrow angle, an attack of acute glaucoma can be caused by dilatation of the pupil. Careful dosing as well as regular and close monitoring is necessary in acute narrow angle glaucoma and raised intraocular pressure.

There is possible worsening of psychotic symptoms when antidepressants are used in patients with schizophrenia or other psychotic disorders. Paranoid thoughts can be intensified.

When the depressive phase of a manic-depressive psychosis is treated, this can turn into the manic phase. Nortriptyline should be stopped if the patient enters a manic phase.

If a sore throat, fever and symptoms of influenza appear in the first ten weeks of the treatment, it is strongly recommended to monitor the blood picture for possible agranulocytosis.

Although antidepressants are not addictive, suddenly interrupting the treatment after long-term administration can cause withdrawal symptoms such as nausea, headache, insomnia, irritability and feeling unwell.

Older patients are often more sensitive to antidepressants, in particular agitation, confusion, orthostatic hypotension and anticholinergic side effects occur.

Anaesthetics can increase the risk of arrhythmias and hypotension during treatment with tri/tetracyclic antidepressants. If possible, nortriptyline should be stopped a few days before an operation; if an emergency operation is unavoidable, the anaesthetist must be made aware of the fact that the patient is being treated with it.

As described for other psychotic agents, nortriptyline can alter the effects of insulin and glucose. This may make it necessary to adjust the antidiabetic therapy in diabetic patients. In addition, the depressive illness itself can affect the patient's glucose balance.

Hyperpyrexia has been reported during treatment with tricyclic antidepressants together with anticholinergics or with neuroleptics, particularly during hot weather.

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

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.

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. Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) are known to be conditions increasing the proarrhythmic risk.'

Serotonin syndrome

Concomitant administration of nortriptyline and opioids (e.g., buprenorphine) and other serotonergic agents, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5).

If concomitant treatment with buprenorphine/opioids and other serotonergic agents 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.

Lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Nortriptyline 25 mg tablets contain Sunset yellow FCF (E110) which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Contraindicated combinations

MAOIs (non-selective and selective A (moclobemide) and selective B (selegiline) – in connection with the risk of serotonin syndrome (see section 4.3).

Combinations advised against

Sympathicomimetics: Nortriptyline can potentiate the cardiovascular effects of adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine and phenylpropanolamine (such as, for example, in local and general anaesthetics and nasal decongestants).

Adrenergic neuron blockers: Tricyclic antidepressants can counteract the antihypertensive effects of guanethidine, betanidine, reserpine, clonidine and methyldopa. It is recommended that all antihypertensive therapy is reconsidered during treatment with tricyclic antidepressants.

Anticholinergics: Tricyclic antidepressants can potentiate the effects of these drugs on the eye, the central nervous system, the intestines and the bladder. Simultaneous use of these drugs must be avoided in connection with an increased risk of paralytic ileus, hyperpyrexia, etc.

Drugs that prolong the QT interval, including antiarrhythmics such as quinidine, the antihistamines astemizole and terfenadine, some antipsychotics (mainly pimozide and sertindol), cisapride, halofantrine and sotalol can increase the risk of ventricular arrhythmias in combination with tricyclic antidepressants.

The tricyclic antidepressants have properties of class I antiarrhythmics. Caution is required in combination with antiarrhythmics of this class, beta-receptor blocking sympathicolytics or calcium antagonists (calcium channel blockers, particularly verapamil) because of a potentiating effect on the AV conduction time and negative inotropy. In combination with class I antiarrhythmics and simultaneous non-potassium-sparing diuretics, there should be awareness of a delaying effect on the QT interval. The serum potassium concentration should be maintained within normal limits.

Use caution when using nortriptyline and methadone concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects.

Thioridazine: Co-administration of nortriptyline 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 nortriptyline 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.

Antimycotics such as fluconazole and terbinafine raise the serum levels of tricyclic antidepressants and the accompanying toxicity. Syncope and torsade de pointes have been reported.

Combinations which require caution when used

Central nervous system depressants: Nortriptyline can potentiate the sedative effect of alcohol, barbiturates and other central nervous system depressants. The sedative effect of antipsychotics, hypnotics, sedatives, anxiolytics and antihistamines is potentiated. Alcohol should be avoided. The dosages of these drugs should be lowered in these cases.

Antidepressants in combination with thyreomimetics can lead to symptoms of hyperthyroidism. Moreover, thyreomimetics can potentiate the antidepressant effect.

The metabolism of levodopa in the intestine is accelerated, possibly due to the slowing of peristalsis.

Delirium has been reported with the concomitant administration of nortriptyline and disulfiram.

Simultaneous administration of nortriptyline and electric shocks can increase the risk of the treatment. Such a treatment should be limited to patients who really need this.

The “serotonin syndrome” (changes in cognition, behaviour, function of the autonomous nervous system and neuromuscular activity) has been reported with nortriptyline when this was administered at the same time as other serotonin-potentiating drugs.

Opioids: Concomitant use of opioids (e.g., buprenorphine) and Nortriptyline may increase the risk of serotonin syndrome, a potentially life-threatening condition (section 4.4).

Pharmacokinetic interactions

Tricyclic antidepressants (TCA) including nortriptyline are primarily metabolised by various hepatic cytochrome P450 isozymes (e.g., CYP1A2, CYP2C, CYP2D6, CYP3A4).

CYP2D6 inhibitors

The CYP2D6 isozyme can be inhibited by a variety of medicinal products, 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 monitoring TCA plasma levels, whenever a TCA is to be co-administered with another medicinal product known to be an inhibitor of CYP2D6. Dose adjustment of nortriptyline 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.

Tricyclic antidepressants and neuroleptics mutually inhibit the metabolism of each other; this may lead to a lowered convulsion threshold, and seizures. It may be necessary to adjust the dosage of these drugs.

Cytochrome P450 inducers
Oral contraceptives, rifampicin, phenytoin, barbiturates, carbamazepine and St. John's Wort (Hypericum perforatum) may increase the metabolism of tricyclic antidepressants and result in lowered plasma levels of tricyclic antidepressants and reduced antidepressant response.

In the presence of ethanol nortriptyline plasma concentrations were increased.

The CYP3A4 and CYP1A2 isozymes metabolise nortriptyline to a lesser extent. However, fluvoxamine (strong CYP1A2 inhibitor) was shown to increase nortriptyline plasma concentrations and this combination should be avoided. Clinically relevant interactions may be expected with concomitant use of nortriptyline and strong CYP3A4 inhibitors such as ketoconazole, itraconazole and ritonavir.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a moderate amount of data from the use of nortriptyline in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Therefore, the drug should not be administered to pregnant patients or women of childbearing age unless the potential benefits clearly outweigh any potential risk.

Following administration in the final weeks of pregnancy, neonatal withdrawal symptoms may occur including irritability, hypertonia, tremors, irregular breathing, weak suckling and possibly anticholinergic symptoms (urine retention, obstipation).

Breast-feeding

Nortriptyline is excreted in limited amounts in breastmilk (corresponding to 0.6 % - 1 % of the maternal dose). Adverse effects for infants have not been reported thus far. Breastfeeding can be continued during nortriptyline therapy if the benefit of the

mother outweighs the potential risk for the infant. Observation of the infant is advised, especially during the first four weeks after birth.

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 lower 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. Patients who are treated with psychotropic medicines may expect a worsening of alertness and attention and should be warned about the potential risk that their ability to drive and use machines may be affected.

4.8 Undesirable effects

Nortriptyline can cause comparable side effects to other tricyclic antidepressants. A number of the side effects listed below (such as headache, tremor, attention disorder, dry mouth, constipation and reduced libido) may also be symptoms of a depression and often decrease as soon as the depressive state of a patient improves.

The side effects of nortriptyline and/or other tricyclic antidepressants are reported by organ system and frequency. The frequencies are given as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000, to <1/100); rare (≥1/10000 to <1/1000); very rare (<1/10000), not known (cannot be estimated from the available data).

Organ system	**Frequency**	**Preferred term (PT)**
Blood and lymphatic system disorders	Rare	Bone marrow depression, agranulocytosis, leukopenia, eosinophilia, thrombocytopenia
Endocrine disorders	Not known	Antidiuretic hormone-secretion deficiency
Metabolism and nutrition disorders	Rare	Reduced appetite
	Not known	Changes of blood sugar levels
Psychiatric disorders	Very common	Aggression
	Common	Confused state, reduced libido
	Uncommon	Hypomania, mania, anxiety, insomnia, nightmares
	Rare	Delirium (in older patients), hallucination
	Not known	Suicidal thoughts and suicidal behaviour[1], agitation, restlessness, aggressive reaction, delusions, orgasm disorder in women, increased libido, disorientation

Nervous system disorders	Very common	Tremor, dizziness, headache
	Common	Attention disorder, dysgeusia, paresthesia, ataxia
	Uncommon	Convulsion
	Rare	Akathisia and dyskinesia
	Not known	Extrapyramidal disorder
Eye disorders	Very common	Accommodation disorder
	Common	Mydriasis
	Very rare	Acute glaucoma
Ear and labyrinth disorders	Uncommon	Tinnitus
Cardiac disorders	Very common	Heart palpitations, tachycardia
	Common	Atrioventricular block, bundle branch block
	Uncommon	Collapse conditions and worsening of cardiac failure
	Rare	Arrhythmia
	Very rare	Cardiomyopathies and Torsade de pointes
	Not known	Hypersensitivity myocarditis
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, constipation, nausea
	Uncommon	Diarrhoea, vomiting, tongue oedema
	Rare	Salivary gland enlargement, paralytic ileus
Hepatobiliary disorders	Uncommon	hepatic impairment (e.g. cholestatic liver disease)
	Rare	Jaundice
	Not known	Hepatitis
Skin and subcutaneous tissue disorders	Very common	Hyperhidrosis
	Uncommon	Rash, urticaria, facial oedema

	Rare	Alopecia, photosensitivity reaction
Renal and urinary disorders	Common	Micturition disorders
	Uncommon	Urinary retention
Reproductive system and breast disorders	Common	Erectile dysfunction
	Uncommon	Galactorrhoea
	Rare	Gynaecomastia
General disorders and administration site conditions	Common	Fatigue, feeling thirst
	Rare	Pyrexia
Investigations	Common	Weight gain, electrocardiogram abnormal, electrocardiogram QT interval prolonged, electrocardiogram QRS complex prolonged, hyponatraemia
	Uncommon	Intraocular pressure raised
	Rare	Weight loss, liver function test abnormal. Blood alkaline phosphatase raised, transaminases raised.

[1]Cases of suicidal ideation and suicidal behaviour have been reported during treatment with nortriptyline or soon after stopping the treatment (see section 4.4)

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 that causes this higher risk is not known.

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, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Doses as low as 50mg (especially in children) may lead to clinically significant symptoms. There are considerable differences between one individual and another in their reaction to an overdose. In adults the ingestion of more than 500 mg has caused moderate to severe poisoning and less than 1000 mg has proved to be fatal. In a deliberate overdose of tricyclic antidepressants, the ingestion of several substances (including alcohol) often occurs. Because the treatment of an overdose is complex and variable, it is recommended that the doctor contacts the national poisons information centre for current information about the treatment. The onset of signs and

symptoms of toxicity after an overdose of a tricyclic antidepressant is rapid, therefore hospital treatment must be started as quickly as possible.

Phenomena

The phenomena can be slow and gradual, or abrupt and sudden. During the initial hours drowsiness or hyperalertness, agitation and hallucinations occur. Anticholinergic symptoms: mydriasis, tachycardia, urine retention, dry mucosa, reduced intestinal peristalsis. Convulsions, fever, sudden depression of the central nervous system, reduced consciousness which can progress to coma, respiratory depression.

Cardiac symptoms: arrhythmias (ventricular tachyarrhythmias, torsade de pointes, ventricular fibrillation). An ECG frequently shows a prolonged PR interval, widening of the QRS complex, QT prolongation, T-wave lowering or inversion, ST segment depression, and different forms of heart block that can lead to cardiac arrest. Widening of the QRS complex usually correlates well with the severity of the toxicity after an overdose. Heart failure, hypotension, cardiogenic shock, metabolic acidosis, hypokalaemia. When waking possible confusion, agitation, hallucinations and ataxia.

Treatment

Admission to a hospital (ICU). Treatment is symptomatic and supportive. Gastric lavage, even in later stages after oral ingestion, and treatment with activated charcoal. Close observation of the patient even in non-complicated situations; observation of the level of consciousness, pulse, blood pressure and respiration. Frequent monitoring of serum electrolytes and blood gases. If necessary, keeping the airways open by intubation. Treatment with respiratory apparatus is advised to prevent respiratory arrest. Continuous ECG monitoring for 3 to 5 days. A wide QRS interval, heart failure or ventricular arrhythmias can respond to alkaline pH in the blood (bicarbonate or average hyperventilation) and a rapid infusion of hypertonic sodium chloride (100-200 mmol Na+). Conventional antiarrythmics can be used, such as lidocaine in ventricular arrhythmias 50-100 mg (1 to 1.5 mg/kg) IV, then 1 – 3 mg/min via IV infusion. Quinidine and procainamide usually should not be used because they may exacerbate arrhythmias and conduction already slowed by the overdose. Cardioversion and defibrillation if necessary. Circulatory failure should be treated with plasma expanders and in serious situations with dobutamine – infusion is initially 2-3 µg/kg per minute with an increasing dose depending on the response. Restlessness and convulsions can be treated with diazepam.

Psychiatric follow-up

Because overdose is often deliberate, patients may attempt suicide in other ways during the recovery phase. Referral to a psychiatrist may be desirable.

Paediatric patients

Children are particularly sensitive to cardiotoxicity and seizures. The doctor is strongly advised to contact a poisons centre for specific advice on treatment in children.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidepressants – Non-selective monoamine uptake inhibitor (tricyclic antidepressant), ATC code: N06AA10

Mechanism of action

Nortriptyline is a tricyclic antidepressant. Nortriptyline, a secondary amine, is also the most active metabolite of amitriptyline. Nortriptyline is a stronger inhibitor of presynaptic noradrenaline reuptake than that of serotonin, while amitriptyline inhibits the reuptake of noradrenaline and serotonin to a similar extent. Nortriptyline is less anticholinergic than amitriptyline but has a fairly strong antihistaminergic effect and it potentiates the effects of catecholamines.

Clinical efficacy and safety

Nortriptyline raises the pathologically depressed mood. On account of its centrally stimulating properties, nortriptyline is of special value in depression where inhibition, apathy and a lack of initiative are characteristics of the disease. The antidepressant effect usually starts to act after 2-4 weeks, while the reduction in inhibition can start considerably earlier.

Among the tricyclic antidepressants nortriptyline can have a particularly low risk of inducing orthostatic hypertension.

5.2 Pharmacokinetic properties

Absorption

Oral administration results in maximum plasma levels after 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 distribution volume (Vd) ß, estimated after intravenous administration is 1633±268 l; range 1460-2030 (21±4 l/kg). The plasma protein binding is approximately 93%. Nortriptyline crosses the placental barrier.

Biotransformation

The metabolism of nortriptyline takes place 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 in which the trans form dominates in the body. N-dimethyl nortriptyline is also formed to a certain extent. The metabolites have the same profile as nortriptyline but are rather weaker. Trans 10-hydroxynortriptyline is more potent than the cis form. In the plasma the quantity of total 10-hydroxynortriptyline dominates but most of the metabolites are conjugated.

Elimination

The elimination half-life (T1/2ß) of nortriptyline after oral 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/hour; range 18.6-39.6 l/hour.

Excretion is mainly via the urine. The renal elimination of unchanged nortriptyline is insignificant (around 2%).

In breast-feeding mothers nortriptyline is excreted in small quantities in the mother's milk. The ratio between milk concentration/plasma concentration in women is 1:2. The estimated daily exposure of the child is on average equivalent to 2% of the dose of nortriptyline related to the mother's weight (in mg/kg)

Steady state plasma levels of nortriptyline are reached within one week for most patients.

Elderly patients

In elderly patients longer half-lives and reduced oral clearance values (Clo) have been seen due to a slower metabolic rate.

Reduced liver function

Liver conditions of a certain degree of severity can reduce the hepatic extraction as a result of which higher plasma levels occur.

Reduced renal function

Kidney failure has no effect on the kinetics.

Polymorphism

The metabolism is subject to genetic polymorphism (CYP2D6)

Pharmacokinetic/pharmacodynamic ratio(s)

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 disturbance of the heart conduction in terms of a prolonged QRS complex or an AV block.

5.3 Preclinical safety data

Tricyclic antidepressants such as nortriptyline can cause teratogenicity in laboratory animals, including cranial abnormalities and encephalocele.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Maize starch

Calcium hydrogen phosphate (E 341)
Magnesium stearate (E 470b)

Coating
Hypromellose (E 464)
Glycerol (E 422)
Sunset Yellow FCF Aluminum Lake (E 110)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Alu-Alu and Alu-PVC/PE/PVDC blister pack:
Pack size: 10, 14, 15, 20, 24, 25, 28, 30, 50, 56, 100 and 150 film-coated tablets.

HDPE bottle pack:
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

Brown & Burk UK Ltd
5 Marryat Close
Hounslow West
Middlesex
TW4 5DQ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 25298/0309

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23/04/2021

10 DATE OF REVISION OF THE TEXT

30/03/2022