SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nortriptyline 25 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Nortriptyline 25 mg Tablets:
Each Tablets contains Nortriptyline Hydrochloride equivalent to 25 mg nortriptyline.

Excipient(s) with known effect
Each tablet contains 107.65 mg lactose monohydrate
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nortriptyline 25 mg Tablets:
Tablet.

Biconvex white round tablets, marked 25 on one side (Diameter: 8.0±0.20mm).

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 as appropriate effect and any sign of intolerability is closely monitored. Dosages higher than 150 mg/day should preferably be limited to hospitalized patients (up to 200-250 mg). The optimal therapeutic plasma level of nortriptyline is 50 - 150 ng/ml.

Adults:
The usual adult dose is 25mg three or four times daily. Dosage should begin at a low level (10 mg three or four times daily) and be increased as required. Alternatively, the total daily dose may be given once a day, usually given at night. When doses above 100 mg daily are administered, plasma levels of nortriptyline should be monitored and maintained in the optimum range of 50 to 150ng/ml. Doses above 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 patients:
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 isoenzymeCYP2D6. 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.

Reduced renal function

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

Reduced hepatic function
In case of reduced liver function careful dosing and, if possible, a serum level determination is advisable.

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).

Duration of treatment
The antidepressant effect usually sets in after 2 - 4 weeks. Treatment with antidepressants is symptomatic and must therefore be continued for an appropriate length of time usually up to 6 months after recovery in order to prevent relapse. In patients with recurrent depression (unipolar) treatment may need to be continued for several years to prevent new episodes prevent.

Discontinuation of treatment
When stopping therapy nortriptyline should be gradually withdrawn over several weeks

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 and coronary artery insufficiency.

Severe liver disease.

Concomitant treatment with MAOIs (monoamine oxidase inhibitors) is contra-indicated (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 the reversible moclobemide.

Treatment with MAOIs may be introduced 14 days after discontinuation of nortriptyline.

4.4 Special warnings and precautions for use

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 patients who exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

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

If possible, the use of nortriptyline should be avoided in patients with narrow angle glaucoma or symptoms suggestive of prostatic hypertrophy

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

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

Cross sensitivity between nortriptyline and other tricyclic antidepressants is a possibility.
Patients with cardiovascular disease should be given nortriptyline only under close supervision because of the tendency of the drug to produce sinus tachycardia and to prolong the conduction time. Myocardial infarction, arrhythmia and strokes have occurred.

With high dose treatment, cardiac arrhythmias and severe hypotension may occur. Patients should be monitored for arrhythmias during high dose therapy. Arrhythmias and severe hypotension may also occur in patients with existing heart disease who are being treated with a normal dose occurs.

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).

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.

Anaesthetics given during tricyclic antidepressant therapy may increase the risk of arrhythmias and hypotension. If possible, discontinue this medicinal product several days before surgery; if emergency surgery is unavoidable, the anaesthetist should be informed that the patient is being so treated (see section 4.5).

Great care is necessary if nortriptyline is administered to hyperthyroid patients or to those receiving thyroid medications, since cardiac arrhythmias may develop.

The use of nortriptyline should be avoided, if possible, in patients with a history of epilepsy. If it is used, however, the patients should be observed carefully at the beginning of treatment, for nortriptyline is known to lower the convulsive threshold.

The elderly are particularly liable to experience adverse reactions, especially agitation, confusion and postural hypotension.

Troublesome hostility in a patient may be aroused by the use of nortriptyline.

If possible, the use of nortriptyline should be avoided in patients with narrow angle glaucoma or symptoms suggestive of prostatic hypertrophy.

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

Use of nortriptyline in the treatment of depressive phase in patients with bipolar disorder may lead to transition to manic phase. In these cases nortriptyline should be discontinued.

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).

Nortriptyline should be used with caution in patients with urinary retention, pylorus stenosis or paralytic ileus.

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

Serotonin syndrome
Co-administration of Nortriptyline and buprenorphine may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5).

If concomitant treatment with 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.

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 MAOIs (see sections 4.3 and 4.5).

Excipients
The tablets contain lactose.
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

Potential for nortriptyline to affect other medicinal products

Nortriptyline should be used cautiously when co-administered with buprenorphine as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

Contraindicated combinations

MAOIs (non-selective as well as selective A (moclobemide) and B (selegiline)) - risk of "serotonin syndrome" (see section 4.3).

Combinations that are not recommended

Sympathomimetic agents

Nortriptyline should not be given with sympathomimetic agents such as adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine and phenylpropanolamine ***(e.g. as contained in local and general anaesthetics and nasal decongestants)***.

Adrenergic neurone blockers/antihypertensives

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 is advisable to review all antihypertensive therapy during treatment with tricyclic antidepressants.

Anticholinergic agents

Tricyclic antidepressants may potentiate the effects of these medicinal products 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.

Drugs which prolong the QT-interval, including antiarrhytmics 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.

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.

Caution is also advised for co-administration of nortriptyline and diuretics inducing hypokalaemia (e.g. furosemide)

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.

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

Combinations requiring precautions for use

CNS depressants: Nortriptyline may enhance the sedative effects of alcohol, ***barbiturates and other CNS depressants.***

Influence of other drugs on the pharmacokinetics of tricyclic antidepressants

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 to monitor 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.

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.

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.

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, tremor, irregular breathing, and possibly anticholinergic symptoms (urinary retention, constipation).

The use of high doses of TCAs in the third trimester may have an effect on the newborn, including behavioural disturbances.

Lethargy has been reported in neonates after use of amitriptyline and urinary retention after use of nortriptyline (a metabolite of amitriptyline) in pregnant women until the end of pregnancy.

In animal studies, adverse effects have been seen at high doses (see section 5.3).

Breast-feeding

Nortriptyline is excreted into breast milk (corresponding to 0.6% - 1% of the maternal dose). The relative child dose is low and the serum concentrations in the infant are low or undetectable. The infant receives approximately 2% of the mother's weight-related daily dose (in mg/kg). 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 months after birth.

Fertility

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

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. 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

In the listing below the following convention is used:
MedDRA system organ class / preferred term

Very common (> 1/10); common (> 1/100, < 1/10); uncommon (> 1/1,000, < 1/100); rare (> 1/10,000, < 1/1,000); very rare (< 1/10,000), not known (can not be estimated from the available data).

Organ System	**Frequency**	**Preferred Term**
Blood and lymphatic system disorders	Rare	Bone marrow depression, agranulocytosis, leucopenia, eosinophilia, thrombocytopenia.
Endocrine disorders	Not Known	Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
Metabolism and nutrition disorders	Rare	Decreased appetite.
	Not Known	changes of blood sugar levels, hyponatraemia
Psychiatric disorders	Very common	Agression
	Common	Confusional state, libido decreased, agitation
	Uncommon	Hypomania, mania, anxiety, insomnia, nightmare.
	Rare	Delirium (in elderly patients), hallucination (in schizophrenic patients).
	Not Known	*Suicidal ideation and suicidal behaviour, Paranoia, restlessness, aggressive reaction, delusions, orgasm disorder in women, increased libido, disorientation
Nervous system disorders	Very common	Tremor, dizziness, headache.
	Common	Disturbance in attention, dysgeusia, paresthesia, ataxia.
	Uncommon	Convulsion.
	Very Rare	akathisia, 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	Palpitations, tachycardia
	Common	Atrioventricular block, bundle branch block.
	Uncommon	Collapse conditions, worsening of cardiac failure
	Rare	Arrhythmia.
	Very rare	Cardiomyopathies, torsades de pointes
	Not known	hyoersensitivty myocarditis, brugada syndrome (unmasking)

Vascular disorders	Very 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, ileus paralytic.
Hepatobiliary disorders	Rare	Jaundice.
	Uncommon	Hepatic impairment (e.g. cholestatic liver disease).
	Not known	Hepatitis
Skin and subcutaneous tissue disorders	Very common	Hyperhidrosis.
	Uncommon	Rash, urticaria, face 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	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 nortriptyline therapy or early after treatment discontinuation (see section 4.4)
Withdrawal symptoms: 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. By reporting side effects you can help provide more information on the safety of this medicine.

4.9 Overdose

Signs and symptoms: 50mg of a tricyclic antidepressant can be an overdose in a child. Of patients who are alive at presentation, mortality of 0-15% has been reported. Symptoms may begin within several hours and may include blurred vision, confusion, restlessness, dizziness, hypothermia, hyperthermia, agitation, vomiting, hyperactive reflexes, dilated pupils, fever, rapid heart rate, decreased bowel sounds, dry mouth, inability to void, myoclonic jerks, seizures, respiratory depression, myoglobinuric renal failure, nystagmus, ataxia, dysarthria, choreoathetosis, coma, hypotension and cardiac arrhythmias. Cardiac conduction may be slowed, with prolongation of QRS complex and QT intervals, right bundle branch and AV block, ventricular tachyarrhythmias (including Torsade de pointes and fibrillation) and death. Prolongation of QRS duration to more than 100msec is predictive of more severe toxicity. The absence of sinus tachycardia does not ensure a benign course. Hypotension may be caused by vasodilatation, central and peripheral alpha-adrenergic blockade and cardiac depression. In a healthy young person, prolonged resuscitation may be effective; one patient survived 5 hours of cardiac massage.

Treatment:
Patients should be admitted to hospital (intensive care unit) and closely monitored even in apparently uncomplicated situations. Treatment is symptomatic and supportive.

LAC (airway, breathing and circulation) should be evaluated and treated as necessary. Airway patency is maintained by intubation if necessary. Treatment with a breathing apparatus is recommended to prevent possible respiratory arrest. Continuous ECG monitoring of cardiac function for 3-5 days is recommended. Urea and electrolytes should be monitored, especially for low potassium. Urine output should be monitored.

Arterial blood gases should be monitored, especially for acidosis. Consider gastric lavage only if it can be performed within one hour of a potentially fatal overdose. Give 50 g of activated charcoal if this can be administered within one hour of taking it.

Treatment of the following matters will be decided on an individual basis:
- Wide QRS intervals, heart failure and ventricular arrhythmias

- Circulatory failure
- Hypotension
- Hyperthermia
- Convulsions
- Metabolic acidosis

Agitation and convulsions can be treated with diazepam.

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

Psychiatric follow-up

Because overdose is often intentional, patients may attempt suicide through other means during the recovery phase. Referral to a psychiatrist may be desirable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidepressants, ATC code: N06AA10

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

5.2 Pharmacokinetic properties

Parts of metabolism of Nortriptyline include hydroxylation (possibly to active metabolites). N-oxidation and conjugation with glucuronic acid. Nortriptyline is widely distributed throughout the body and is extensively bound to plasma and tissue protein. Plasma concentrations of Nortriptyline vary very widely between individuals and no simple correlation with therapeutic response has been established.

5.3 Preclinical safety data

Nortriptyline inhibits ion channels, which are responsible for cardiac conduction (SCN5A- and hERG channels), in the upper micromolar range of therapeutic plasma concentrations. Therefore, nortriptyline may increase the risk for cardiac arrhythmia (see section 4.4).

Nortriptyline did not show any mutagenic potential.

The reproductive toxicity of nortriptyline has not been investigated in animals. For its parent substance amitriptyline, teratogenic effects and developmental delays have been only observed at high dosages**.** There was also 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

Maize Starch
Lactose Monohydrate
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister Pack:
PVDC/PVC-Al white opaque blister
Pack size(s): 7, 10, 14, 15, 20, 25, 28, 30, 42, 45, 50, 56, 60, 70, 75, 84, 90, 98, and 100 tablets.

PA/Al/PVC-Al blister
Pack size(s): 10, 20, 30, 40, 50, 60, 70, 80, 90, and 100 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

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

7 MARKETING AUTHORISATION HOLDER

Crescent Pharma Limited
Key House, Sarum Hill,
Basingstoke,
RG21 8SR,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20416/0793

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/12/2020

10 DATE OF REVISION OF THE TEXT

13/09/2024