SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nortriptyline 50 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50 mg nortriptyline (as Nortriptyline hydrochloride).

Excipient with known effect

Each film-coated tablet contains 218.26 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White to off white coloured, film coated, round, biconvex tablets with debossing ‘U16’ on one side and plain on other side. (Dimension: 10.1 ± 0.2 mmX4.9 ± 0.3 mm)

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 e.g. 10mg 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 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. Lower dosages are also recommended for outpatients than for hospitalised patients who will be under close supervision. The physician should initiate dosage at a low level and increase it gradually, noting carefully the clinical response and any evidence of intolerance. Following remission, maintenance medication may be required for a longer period of time at the lowest dose that will maintain remission.

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

The elderly: 30 to 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.

<u>Cytochrome P450 isoenzyme CYP2D6 and poor metabolisers</u>

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.

<u>Reduced renal function</u>

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

<u>Reduced hepatic function</u>

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.

Discontinuation of treatment

When stopping therapy nortriptyline should be gradually withdrawn over several weeks.

Method of administration

For oral administration.

Swallow whole with a glass of water.

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 (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.

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

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 those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old. Close supervision of patients and in particular those at high risk should accompany drug therapy in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need
to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

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

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

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

Caution should be exercised when treating patients with advance liver disease.

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

Cardiac arrhythmias are likely to occur with high dosage. They may also occur in patients with pre-existing 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).

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.

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.

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).

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).

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.

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)

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

If concomitant treatment with buprenorphine containing medicinal products 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.

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.

Excipients

Nortriptyline 10mg Film-coated Tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose galactose malabsorption should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium free’.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindicated combinations

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

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).**

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 agent

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 tricyclicantidepressants (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.

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.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

For Nortriptyline only limited clinical data are available regarding exposed pregnancies.

For its parent substance amitriptyline animal studies have shown reproductive toxicity (see section 5.3).

Amitriptyline not recommended during pregnancy unless clearly necessary and only after careful 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, irregular breathing, poor drinking and loud crying and possibly anticholinergic symptoms (urinary retention, constipation).

Breast-feeding

Nortriptyline is 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 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 to <1/10); uncommon (≥ 1/1,000 to <1/100); rare (≥ 1/10,000 to <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.*
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*	*aggression*
	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*

Nervous system disorders	*Very common*	*Tremor, dizziness, headache.*
	Common	*Disturbance in attention, dysgeusia, paraesthesia, ataxia.*
	Uncommon	*Convulsion.*
	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	*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, constipation, nausea.*
	Uncommon	*Diarrhoea, vomiting, tongue oedema.*
	Rare	*Salivary gland enlargement, ileus*

		paralytic
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, face oedema.*
	Rare	*Alopecia, photosensitivity reaction.*
Renal and urinary disorders	*Uncommon*	*Urinary retention.*
	Common	*Micturition disorders*
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 increase*
	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 SSRs and TCAs. The mechanism leading to this risk is unknown.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important.

It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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.

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. Activated charcoal may be more effective than emesis or lavage to reduce absorption.

Ventricular arrhythmias, especially when accompanied by lengthened QRS intervals, may respond to alkalinisation by hyperventilation or administration of sodium bicarbonate. Serum electrolytes should be monitored and managed. Refractory arrhythmias may respond to propranolol, bretylium or lignocaine. Quinidine and procainamide usually should not be used because they may exacerbate arrhythmias and conduction already slowed by the overdose.

Seizures may respond to diazepam. Phenytoin may treat seizures and cardiac rhythm disturbances. Physostigmine may antagonise atrial tachycardia, gut

immotility, myoclonic jerks and somnolence. The effects of physostigmine may be short-lived.

Diuresis and dialysis have little effect. Haemoperfusion is unproven. Monitoring should continue, at least until the QRS duration is normal.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidepressants, ATC code: N06AA10

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

In the treatment of depression Nortriptyline is given by mouth as the hydrochloride in doses equivalent to Nortriptyline 10mg 3 or 4 times daily initially, gradually increased to 25mg 4 times daily as necessary. A suggested initial dose for adolescents and the elderly is 10mg thrice daily. Inappropriately high plasma concentrations of Nortriptyline have been associated with deterioration in antidepressant response. Since Nortriptyline has prolonged half-life, once daily dosage regimens are also suitable, usually given at night.

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

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 inhibited ion channels, which are responsible for cardiac repolarization (hERG channels), in the upper micromolar range of therapeutic plasma concentrations. Therefore, nortriptyline may increase the risk for cardiac arrhythmia (see section 4.4).

For its parent substance amitriptyline the genotoxic potential 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.

The reproductive toxicity of nortriptyline has not been investigated in animals, for its parent substance amitriptyline 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

Tablet core:

Lactose Monohydrate (E473),

Dicalcium Phosphate dihydrate,

Pregelatinized Starch,

Colloidal silicon dioxide,

Croscarmellose sodium (E468),

Magnesium Stearate (E572)

Coating:

Hypromellose (E464),

Triacetine (E1518),

Titanium dioxide (E171),

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Blister packs of Aluminium foil and clear PVC/ PVDC film containing 30 or 100 film-coated 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

Macleods Pharma UK Limited,

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TS22 5TB, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 34771/0265

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29/11/2022

10 DATE OF REVISION OF THE TEXT

23/04/2024