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 of nortriptyline (as hydrochloride).

Excipient(s) with known effect: Lactose monohydrate
Each film coated tablet contains 123.420 mg lactose monohydrate
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated Tablet

Peach coloured, circular, biconvex film coated tablet plain on both sides.

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 and be increased as required. Alternatively, the total daily dose may be given once a day usually 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 50 mg/day in divided doses. Dosage should begin at a low level (10 – 20 mg daily) and be increased as required to the maximum dose of 50mg. If it is considered necessary to use higher dosing in an elderly patient an ECG should be checked and plasma levels of nortriptyline should be monitored.

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 P450IID6 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.

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.

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.
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.

Severe liver disease.
Mania.

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.

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 behavior with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (an caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behavior 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.

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. Great care is necessary if nortriptyline is administered to hyperthyroid patients or to those receiving thyroid medications, 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.

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.

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

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.

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.)

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).

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

4.5 Interaction with other medicinal products and other forms of interaction

Drug interactions: Under no circumstances should Nortriptyline be given concurrently with, or within two weeks of cessation of, therapy with monoamine oxidase inhibitors. Hyperpyretic crises, severe convulsions and fatalities have occurred when similar tricyclic antidepressants were used in such combinations.

Nortriptyline should not be given with sympathomimetic agents such as adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine and phenylpropanolamine.

Nortriptyline may decrease the antihypertensive effect of guanethidine, debrisoquine, bethanidine and possibly clonidine. Concurrent administration of reserpine has been shown to produce a 'stimulating' effect in some depressed patients. It would be advisable to review all antihypertensive therapy during treatment with tricyclic antidepressants.

Barbiturates may increase the rate of metabolism of Nortriptyline.

Anaesthetics given during tricyclic antidepressant therapy may increase the risk of arrhythmias and hypotension. If surgery is necessary, the drug should be discontinued, if possible, for several days prior to the procedure, or the anaesthetist should be informed if the patient is still receiving therapy.

Tricyclic antidepressants may potentiate the CNS depressant effect of alcohol. The potentiating effect of excessive consumption of alcohol may lead to increased suicidal attempts or overdosage, especially in patients with histories of emotional disturbances or suicidal ideation.

Steady-state serum concentrations of the tricyclic antidepressants are reported to fluctuate significantly as cimetidine is either added to or deleted from the drug regimen. Higher than expected steady-state serum concentrations of the tricyclic antidepressant have been observed when therapy is initiated in patients already taking cimetidine. A decrease may occur when cimetidine therapy is discontinued.

Because Nortriptyline's metabolism (like other tricyclic and SSRI antidepressants) involves the hepatic cytochrome P450IID6 isoenzyme system, concomitant therapy with drugs also metabolised by this system may lead to drug interactions. Lower doses than are usually prescribed for either the tricyclic antidepressant or the other drug may therefore be required.

Greater than two-fold increases in previously stable plasma levels of nortriptyline have occurred when fluoxetine was administered concomitantly. Fluoxetine and its active metabolite, norfluoxetine, have long half-lives (4-16 days for norfluoxetine).

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

Concomitant therapy with other drugs that are metabolised by this isoenzyme, including other antidepressants, phenothiazines, carbamazepine, propafenone, flecainide and encainide, or that inhibit this enzyme (eg, quinidine), should be approached with caution.

Supervision and adjustment of dosage may be required when nortriptyline is used with other anticholinergic drugs.

4.6 Fertility, pregnancy and lactation

Pregnancy

For Notriptyline 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 is 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

Included in the following list are a few adverse reactions that have not been reported with this specific drug. However, the pharmacological similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when Nortriptyline is administered.

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
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, paresthesia, 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
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: Though these are not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache and malaise.

Class Effects: Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving 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 Yellow Card Scheme at: 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

Individual differences in metabolism may lead to symptoms and signs of overdose even after relatively modest excess ingestion, irrespective of age.

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

Nortriptyline has prolonged half-life, once daily dosage regimens are also suitable, usually given at night.

5.2 Pharmacokinetic properties

The elimination half-life (t 1/2 β) after oral nortriptyline administration is approximately 26 hours (25.5 ± 7.9 hours; range 16-38 hours). The mean systemic clearance (Cls) is 30.6 ± 6.9 l/h; ranging from 18.6 to 39.6 l/hour. Excretion is mainly via the urine. The renal elimination of unchanged nortriptyline is insignificant (about 2%).

In lactating mothers, nortriptyline is excreted in small quantities into breast milk. The concentration ratio of milk/plasma concentration in women is 1:2. The estimated daily infant exposure is on average equivalent to 2% of the maternal weight-related dose of nortriptyline (mg/kg). Steady state plasma levels of nortriptyline for most patients are reached within one week.

In elderly patients, longer half-lives and reduced oral clearance (CLO) values due to reduced metabolic rate have been shown.

Moderate to severe liver disease may reduce hepatic clearance resulting in higher plasma levels.

Renal failure has no significant effect on nortriptyline kinetics.

Pharmacokinetic / pharmacodynamic relationship

The therapeutic plasma concentration in endogenous depression is 50-140 ng/ml (~190-530 nmol/1).
Levels above 170-200 ng/ml are associated with an increased risk of cardiac conduction disturbance in terms of a prolonge QRS complex or an AV block.

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:

Cellulose microcrystalline,

Lactose monohydrate,

Maize starch,

Silica colloidal anhydrous (E551),

Magnesium stearate (E572)

Coating:

Isopropyl alcohol,

Dichloromethane,

Instamoistshield A21E01392 (Peach) which contains Hypromellose (E464),

Diethyl phthalate,

Ethyl cellulose (E462),

Talc (E553b),

Titanium dioxide (E171),

Red iron oxide (E172)

Yellow iron oxide (E172)

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

30 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium-PVC/PVDC blister packs of 30 tablets.

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

Flamingo Pharma UK Ltd.
1st floor, Kirkland House,
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8 MARKETING AUTHORISATION NUMBER(S)

PL 43461/0069

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT

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