SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nortriptyline Colonis 25mg/ 5ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of Nortriptyline Colonis 25mg/ 5 ml Oral Solution contains 25mg Nortriptyline (as Nortriptyline Hydrochloride).

Excipient(s) with known effect

Each 1 ml of Nortriptyline Colonis Oral Solution contains 0.50mg sodium benzoate and 0.08mg sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral Solution
Clear colourless and odourless solution.

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 for example 10mg three to 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.

Note: For doses over 20mg, Nortriptyline Colonis 25mg/5ml Oral Solution should be used.

Lower than usual dosages are recommended for elderly patients (see section 5.2).

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 P450IID6. Three to ten per cent of the population have reduced isoenzyme activity ('poor metabolisers') and may have higher than expected plasma concentrations at usual doses. The percentage of 'poor metabolisers' in a population is also affected by its ethnic origin (see section 5.2).

<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.

A double-ended dosing spoon is provided with the product. The small spoon measures a 2.5 ml dose and the larger spoon measures 5 ml.

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.

Concomitant use with monoamine oxidase inhibitors and sympathomimetic agents is contraindicated (see section 4.5).

Severe liver disease

Mania

Nortriptyline is contraindicated for the nursing mother and for children under the age of six years.

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 especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Withdrawal symptoms, including insomnia, irritability 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, for this reason nortriptyline should not be given to these patients (see section 4.3).
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 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.

<u>QT interval prolongation</u>
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.

<u>Serotonin Syndrome</u>
Concomitant administration of Nortriptyline Colonis 10mg/ 5ml Oral Solution and buprenorphine and buprenorphine, naloxone may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5). If concomitant treatment with buprenorphine and buprenorphine, naloxone is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.
If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

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

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

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 and section 4.9).

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.

Nortriptyline Colonis 25mg/5ml Oral Solution contains sodium benzoate and sodium.

This medicine contains 0.50 mg sodium benzoate in each ml.

This medicine contains less than 1 mmol sodium (23 mg) per 30ml oral solution, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindicated combinations

Drug interactions: Under no circumstances should nortriptyline be given concurrently with, or within two weeks (14 days) of cessation of, therapy with monoamine oxidase inhibitors (MAOIs). Simultaneous administration of nortriptyline and MAOIs may cause serotonin syndrome. Hyperpyretic crises, severe convulsions and fatalities have occurred when similar tricyclic antidepressants were used in such combinations. 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 (see section 4.3).

Combinations not recommended

Sympathomimetic agents

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

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

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.

Barbiturates may increase the rate of metabolism of nortriptyline.
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.

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, obstipation).

Breast-feeding

Nortriptyline is excreted into breast milk. Nortriptyline is contraindicated for the nursing mother (see section 4.3).

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 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, leucopoenia, eosinophilia, thrombocytopenia
	Not known	aplastic anaemia
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 (especially in the elderly) disorientation, delusion, restlessness, panic disorder, psychotic disorder, libido decreased/increased, 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, numbness, tingling, incoordination peripheral neuropathy, seizures, alteration of EEG patterns
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, myocardial infarction, cerebrovascular accident
Vascular disorders	Common	Orthostatic hypotension
	Uncommon	Hypertension
	Not known	Hyperthermia, flushing
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
	Not known	Dyspepsia, stomatitis, abdominal pain, tongue discoloration, rarely associated sublingual adenitis or gingivitis
Hepatobiliary disorders	Uncommon	Hepatic impairment (e.g. cholestatic liver disease)
	Rare	Jaundice
	Not known	Hepatitis, liver necrosis
Skin and subcutaneous tissue disorders	Very common	Hyperhidrosis
	Uncommon	Rash, urticaria, face oedema
	Rare	Alopecia, photosensitivity reaction
	Not known	Purpura, petechiae
Renal and urinary disorders	Uncommon	Urinary retention
	Common	Micturition disorders
	Not known	Pollakiuria, nocturia
Reproductive system and breast disorders	Common	Erectile dysfunction
	Uncommon	Galactorrhoea
	Rare	Gynaecomastia
	Not known	Testicular swelling
General disorders and administration site conditions	Common	Fatigue, feeling thirst
	Rare	Pyrexia
	Not known	Asthenia
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 Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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

Signs and symptoms: Of patients who are alive at presentation, mortality of 0-15% has been reported. Symptoms may begin within several hours and may include blurred vision, confusion, restlessness, dizziness, hypothermia, hyperthermia, agitation, vomiting, hyperactive reflexes, dilated pupils, fever, rapid heart rate, decreased bowel sounds, dry mouth, inability to void, myoclonic jerks, seizures, respiratory depression, myoglobinuric renal failure, nystagmus, ataxia, dysarthria, choreoathetosis, coma, hypotension and cardiac arrhythmias. Cardiac conduction may be slowed, with prolongation of QRS complex and QT intervals, right bundle branch and AV block, ventricular tachyarrhythmias (including Torsade de pointes and fibrillation) and death. Prolongation of QRS duration to more than 100msec is predictive of more severe toxicity. The absence of sinus tachycardia does not ensure a benign course. Hypotension may be caused by vasodilatation, central and peripheral alpha-adrenergic blockade and cardiac depression. In a healthy young person, prolonged resuscitation may be effective; one patient survived 5 hours of cardiac massage.
Treatment: Symptomatic and supportive therapy is recommended. Early transfer to a hospital with an intensive care unit is recommended. Activated charcoal may be more effective than emesis or lavage to reduce absorption, although combination therapy may be appropriate depending on the time since ingestion.
Ventricular arrhythmias, especially when accompanied by lengthened QRS intervals, may respond to alkalinisation by hyperventilation or administration of sodium bicarbonate or the rapid infusion of hypertonic sodium chloride (100-200mmol). Serum electrolytes should be monitored and managed.

Refractory arrhythmias may respond to propranolol, bretylium or lignocaine (usually 1-1.5mg/kg iv followed by 1-3mg/min). Quinidine and procainamide usually should not be used because they may exacerbate arrhythmias and conduction already slowed by the overdose.
Seizures may respond to diazepam. Phenytoin may treat seizures and cardiac rhythm disturbances. Physostigmine may antagonise atrial tachycardia, gut immotility, myoclonic jerks and somnolence. The effects of physostigmine may be short-lived.
Diuresis and dialysis have little effect. Haemoperfusion is unproven.
Monitoring should continue, at least until the QRS duration is normal.
Doses as low as 50mg (especially in children) may lead to clinically significant symptoms.

Cardiotoxicity and convulsions are commoner in children and toxicological advice is recommended in all cases.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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.

Mechanism of action
Nortriptyline blocks the uptake of norepinephrine and to a lesser extent that of serotonin. It blocks cholinergic muscarinic receptors and to a lesser extent, those of alpha1-adrenergic receptor and H1-histamine receptors.

Pharmacodynamic effects
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. Inappropriately high plasma concentrations of nortriptyline have been associated with deterioration in antidepressant response. Since nortriptyline has a prolonged half-life, once daily dosage regimens are also suitable, usually given at night.

The mechanism of mood elevation by tricyclic antidepressants is at present unknown. Nortriptyline is not a monoamine oxidase inhibitor. It inhibits the activity of such diverse agents as histamine, 5-hydroxytryptamine, and acetylcholine. It increases the pressor effect of norepinephrine but blocks the pressor response of phenethylamine. Studies suggest that nortriptyline interferes with the transport, release, and storage of catecholamines. Operant conditioning techniques in rats and pigeons suggest that nortriptyline has a combination of stimulant and depressant properties.

5.2 Pharmacokinetic properties

Absorption

Oral administration results in maximum plasma concentrations in approximately 5 hours (Tmax = 5.5 ±1.9 hours; range 4.0 - 8.8 hours). Bioavailable dose of 51 % and a fraction absorbed of 100 % have been reported. The difference is attributed to the extensive first pass effect.

The availability of nortriptyline was assessed in three healthy subjects by comparing the areas under the plasma concentration versus time curves after oral and intramuscular administration of identical doses of the hydrochloride salt. The observed availability in these subjects ranged between 56 and 70 % (mean of 64 %). Complete GI absorption of nortriptyline is suggested by the fact that the recovery of the main urinary metabolite, 10-hydroxynortriptyline, was essentially the same following both routes of administration. The results suggest that, in humans, a significant fraction of the absorbed drug is lost to the systemic circulation during the first pass through the liver.

Distribution

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.

Nortriptyline is distributed into milk and its concentrations in milk appear to be similar to or slightly greater than those present in maternal serum.

Biotransformation

The bioavailability of nortriptyline varies from between 0.17 and 0.71, depending on the genotype of the cytochrome P450 (CYP) 2D6.

Nortriptyline is metabolized via a phase I reaction in the liver by the cytochrome P450 isoenzyme 2D6 (CYP2D6) to mainly E-10-hydroxynortriptyline and to a minor extent the stereoisomer Z-10-hydroxynortriptyline. Both metabolites are active re-uptake inhibitors of norepinephrine.

There are conflicting data on nortriptyline behaviour in the elderly. Whether CSS in healthy elderly people will be consistently higher than in a young population for a given dose is not yet established. Those with concurrent medical illness do seem to have higher than expected concentrations, but whether adverse effects are linked to plasma concentrations is also unclear.

Elimination

The plasma half-life of nortriptyline ranges from 16 to more than 90 hours. Nortriptyline is metabolized via the same pathways as are other tricyclic antidepressants. Approximately one-third of a dose of nortriptyline is excreted in urine as metabolites within 24 hours, and small amounts are excreted in faeces via biliary elimination.

Linearity/non-linearity

Within individuals, the steady-state level of nortriptyline in plasma is directly proportional to the administered daily dose. Proportionality between dose und steady-state nortriptyline plasma levels was found both during initial treatment and after long-term treatment (years) within the nortriptyline plasma level range of 20 to 296 ng/ml.

A non-linear (dose-dependent) relationship between dose and plasma-nortriptyline concentrations has been observed during therapeutic drug monitoring in subjects who were considered to be extensive metabolisers of debrisoquine; non-linearity did not appear to occur in poor metabolisers.

Paediatric population

The pharmacokinetic parameters of nortriptyline in the paediatric age group following oral administration of a single dose of 25 or 50 mg were investigated from nortriptyline plasma level assays at 12, 18, 24, 36, and 48 hours post-dose. Data were analysed separately for the nine prepubertal and 11 postpubertal subjects, all of whom were diagnosed major depressive disorder. These data were compared with studies in the literature of nortriptyline pharmacokinetics from adult and geriatric normal and depressed populations. Similar to adults, the elimination of nortriptyline in children and adolescents is apparently first order kinetics with a logarithmically linear rate of disappearance. The prepubertals had a shorter mean half-life (17.6 ±- 3.7 hours) than some adult groups and twice a day dosage would, therefore, be more appropriate for many children. Although the mean half-life (27.1 ± 17.1 hours) for the adolescent group suggested that once a day dosage would be sufficient, some adolescents would need twice a day dosage for optimum plasma level control because there was a wide range (14.1 to 76.2 hours). The almost two-fold variation in half-life in prepubertals and five-fold variation in postpubertals were similar to differences in adult groups and emphasize the value of plasma level monitoring in the clinical use of nortriptyline.

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

Sodium Benzoate (E 211)
Sucralose
Hydrochloric acid(for pH adjustment)
Purified Water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months.
After first opening use within 3 months.

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Amber, type III glass bottles of 250 ml nominal capacity, suitable for pharmaceutical use, safely closed with a child-resistant, screw cap with tamper evident closure.

A 2.5ml/5ml double-ended dosing spoon is also provided to measure the dose.

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

Colonis Pharma Limited
25 Bedford Square
Bloomsbury
London
WC1B 3HH
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8 MARKETING AUTHORISATION NUMBER(S)

PL 41344/0052

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24/03/2025

10 DATE OF REVISION OF THE TEXT

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