

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Nortriptyline Chanelle Medical 10 mg film-coated tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg nortriptyline (as hydrochloride).

Excipient(s) with known effect:

Lactose, 58.42 mg per tablet

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Film-coated tablet.

The 10 mg tablets are white, film-coated, circular, with "C" on one side and "1" on the other side. They are approximately 6 mm in diameter.

## 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 25 mg 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 100 mg daily are administered, plasma levels of nortriptyline should be monitored and maintained in the optimum range of 50 to 150 ng/ml. Doses above 150 mg 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 and coronary insufficiency.
- Severe liver disease
- Mania.
- 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 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.

Due to the risk of suicide, especially at the beginning of treatment, only a limited amount of this medicine should be given to the patient at any one time.

Nortriptyline should not be used in conjunction with an MAOIs (see sections 4.3 and 4.5).

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.

#### 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 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 with buprenorphine should be considered depending on the severity of the symptoms.

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.

#### Other special warnings and precautions for use Nortriptyline

Cardiac arrhythmias and severe hypotension are likely to occur with high dosage. They may also occur in patients with pre-existing heart disease taking normal dosage.

Nortriptyline should be used with caution in patients with convulsions, micturition disorders /urinary retention, prostatic hypertrophy, hyperthyroidism, paranoid symptoms and advanced hepatic or cardiovascular disease.

Caution is advised due to the risk of cardiac arrhythmias when nortriptyline is administered to patients with hyperthyroidism or receiving thyroid medication.

#### 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.

If a sore throat, fever and symptoms of influenza occur during treatment, it is strongly recommended that blood counts are monitored for possible agranulocytosis.

Although antidepressants are not addictive, abrupt discontinuation of treatment after long-term administration may cause withdrawal symptoms such as nausea, headache, insomnia, irritability and malaise.

When it is essential, nortriptyline may be administered with electroconvulsive therapy, although the hazards may be increased.

As described for other psychotropics nortriptyline may modify insulin and glucose responses. This may require adjustment of anti-diabetic therapy in diabetic patients. In addition, the depressive illness itself may affect patients' glucose balance

In addition, the depressive illness itself can also influence the glucose balance of the patient.

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 malabsorption should not take this medicine.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

##### **Pharmacodynamic Interactions**

###### Contraindicated combinations

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

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

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.

###### Combinations not recommended

###### *Sympathomimetics:*

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

###### *Adrenergic neuron blockers:*

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.

###### *Anticholinergics:*

Tricyclic antidepressants can override the effects of these drugs on the eye, central nervous system, bowel and bladder. Concomitant use with these drugs should be avoided because of 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 risk of ventricular arrhythmias in combination with tricyclic antidepressants.

The tricyclic antidepressants have properties of class I antiarrhythmics. Caution is required in combination with anti-arrhythmic drugs of this class, beta-adrenergic receptor blockers or calcium channel blockers (calcium current blocking means, in particular verapamil) due to a potentiating effect on the AV-conduction time and negative inotropy. In combination with Class I antiarrhythmic drugs and concomitant potassium-depleting diuretics, one should be prepared for a retarding effect on the QT interval. The serum potassium concentration should be kept within normal limits.

#### Combinations requiring precautions for use

##### *Central Nervous System Suppressors:*

Nortriptyline may enhance the sedative effect of alcohol, barbiturates and other central nervous system depressants. The sedative effect of antipsychotics, hypnotics, sedatives, anxiolytics and antihistamines is enhanced. Alcohol should be avoided. The dosage of the mentioned drugs should be reduced if necessary.

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.

Antidepressants in combination with antithyroid drugs can cause symptoms of hyperthyroidism. Incidentally, thyromimetics may enhance the anti-depressive effect.

The gut metabolism of levodopa is accelerated, possibly due to a slowing of peristalsis.

Delirium has been reported with co-administration of nortriptyline and disulfiram.

Tricyclic antidepressants may increase the risk of seizures in patients taking tramadol

#### **Pharmacokinetic Interactions**

Influence of other drugs on the pharmacokinetics of tricyclic antidepressants

Tricyclic antidepressants, including nortriptyline, are metabolized by the hepatic cytochrome P450 enzyme CYP2D6. CYP2D6 is polymorphic in the population. The CYP2D6 isoenzyme can be inhibited by various psychotropic or other drugs, such as neuroleptics, serotonin reuptake inhibitors other than citalopram (which is a very weak inhibitor), beta blockers and newer antiarrhythmics. These drugs can significantly decrease it trigger the metabolism of tricyclic antidepressants, which can lead to a significant increase in plasma levels.

Oral contraceptives, phenytoin, carbamazepine and barbiturates, due to their effect on the liver, induce an acceleration of the metabolism of the antidepressants. As a result, plasma levels may be reduced and the antidepressant effect may be reduced.

Cimetidine, methylphenidate and calcium-channel blockers increase the 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 dose of these medicines.

Antifungals such as fluconazoles and terbinafine have been reported to increase plasma levels of amitriptyline and nortriptyline.

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

#### **4.6 Fertility, pregnancy and lactation**

Pregnancy

A moderate amount of data in pregnant women indicates no malformative or feto/neonatal toxicity of Nortriptyline. Animal studies have shown reproductive toxicity (see section 5.3). Nortriptyline should only be used when strictly indicated.

The kinetics of nortriptyline changes during pregnancy, especially during the 2<sup>nd</sup> and 3<sup>rd</sup> trimesters. Therefore, serum levels should be monitored and the dose should be adjusted if needed. After chronic use and administration near term, neonatal withdrawal symptoms (irritability, hypertonus, tremors, irregular breathing, weak suckling) and anticholinergic symptoms (urine retention, constipation) may occur.

Breast-feeding

Nortriptyline is excreted in limited amounts. The relative infant dose is low and serum levels have been reported as low or undetectable. Adverse effects on the suckling infant have not been reported to date. Nortriptyline can be used during lactation if the expected benefit for the mother outweighs the potential risk to the infant.

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 ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $<1/10$ ); uncommon ( $\geq 1/1,000$  to  $<1/100$ ); rare ( $\geq 1/10,000$  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 continues monitoring of the benefit/risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected adverse reactions via: HPRA Pharmacovigilance. Website: [www.hpra.ie](http://www.hpra.ie)

### 4.9 Overdose

Individual differences in metabolism may lead to symptoms and signs of overdose even after relatively modest excess ingestion, irrespective of age. Children are especially susceptible to cardiotoxicity and seizures. 50mg of a tricyclic antidepressant can be an overdose in a child.

In adults a more than 500 mg have caused moderate to serious intoxication and less than 1000 mg has been fatal. Of patients who are alive at presentation, mortality of 0-15% has been reported.

Ingestion of multiple substances (including alcohol) is common in intentional overdose with tricyclic antidepressants. Toxicity occurs rapidly following a tricyclic antidepressant overdose, therefore hospital care should be instituted as soon as possible.

*Signs and symptoms:*

The symptoms can occur slowly and insidiously abruptly and surprisingly. During the first hours somnolence or excitation, agitation and hallucinations occur. Anticholinergic symptoms: mydriasis, tachycardia, urinary retention, dry mucous membranes, reduced bowel motility. Convulsions, fever, sudden occurrence of central nervous system depression. Lowered consciousness progressing into coma, respiratory depression.

*Cardiac Symptoms:*

Arrhythmias (ventricular tachyarrhythmias, torsades de pointes, ventricular fibrillations). An ECG often shows a prolonged PR interval, widening of the QRS-complex, QT prolongation, T-wave flattening or inversion, ST segment depression, and varying degrees of heart block progressing to cardiac arrest. Widening of the QRS complex usually correlates well with the severity of toxicity following acute overdoses. Heart failure, hypotension, cardiogenic shock. Metabolic acidosis, hypokalemia. 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.

Confusion, agitation, hallucinations, and ataxia may occur while awake.

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. Symptomatic and supportive therapy is recommended.

ABC's (airway, respiration and circulation) should be assessed and treated as appropriate. Patency of the airway is maintained by intubation, where required. Treatment with a respirator is advised to prevent a possible respiratory arrest.

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

Continuous ECG monitoring of cardiac function for 3-5 days is advised. Ventricular arrhythmias, especially when accompanied by lengthened QRS intervals, may respond to alkalisation by hyperventilation or administration of sodium bicarbonate. Urea and serum electrolytes in particular for low potassium should be monitored and managed. Urine output should be monitored. Arterial blood gases must be checked, in particular for acidosis. 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.

Consider gastric lavage only if within one hour of a potentially fatal overdose. Give 50 g of activated charcoal if it can be administered within one hour of ingestion.

Treatment of the following will be decided on a case-by-case basis:

- Wide QRS intervals, heart failure and ventricular arrhythmias
- Circulatory failure
- Hypotension
- Hyperthermia
- Convulsions
- Metabolic acidosis
- Agitation and convulsions can be treated with 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, Non-selective monoamine uptake inhibitor (tricyclic antidepressant); ATC code: N06AA10

#### Mechanism of action

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

Nortriptyline itself is a stronger inhibitor of pre-synaptic noradrenaline reuptake than of serotonin, and is less anticholinergic than amitriptyline whilst having stronger antihistaminergic effects.

#### Clinical Efficacy and Safety

Nortriptyline increases the pathologically lowered mood level. Because of its centrally stimulating properties, nortriptyline is of special value in depression where inhibition, apathy and lack of initiative are hallmarks of the disease. The antidepressant effect usually sets in after 2-4 weeks, while the release of the inhibition can start considerably earlier.

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

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

### 5.2 Pharmacokinetic properties

#### **Absorption**

Oral administration results in maximum plasma levels after approximately 5 hours ( $T_{max} = 5.5 \pm 1.9$  hours; range 4.0-8.8 hours). Mean oral bioavailability is 51% ( $F_{abs} = 0.51 \pm 0.05$ ; range 0.46-0.59).

#### **Distribution**

The apparent volume of distribution ( $V_d$ )  $\beta$  estimated after intravenous administration is  $1633 \pm 268$  l; range 1460-2030 ( $21 \pm 4$  l / kg). Plasma protein binding is approximately 93%. Nortriptyline crosses the placental barrier.

#### **Biotransformation**

Nortriptyline metabolism occurs by demethylation and hydroxylation followed by conjugation with glucuronic acid. Metabolism is subject to genetic polymorphism (CYP2D6). The main active metabolite is 10-hydroxynortriptyline, which exists in a cis and a trans form with the trans form dominating in the organism. N-demethylnortriptyline is also formed to some extent. The metabolites have the same profile as nortriptyline but are somewhat weaker. Trans 10-hydroxynortriptyline is more potent than the cis form. In plasma, the amount of total 10-hydroxynortriptyline dominates, but most of the metabolites are conjugated.

#### **Elimination**

The elimination half-life ( $t_{1/2}$ )  $\beta$  after oral nortriptyline administration is approximately 26 hours ( $25.5 \pm 7.9$  hours; range 16-38 hours). The mean systemic clearance (Cl) is  $30.6 \pm 6.9$  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.

Polymorphism

Metabolism is subject to genetic polymorphism (CYP2D6).

#### Pharmacokinetic / pharmacodynamic relationship

The therapeutic plasma concentration in endogenous depression is 50-140 ng/ml (~190-530 nmol/l).

Levels above 170-200 ng/ml are associated with an increased risk of cardiac conduction disturbance in terms of a prolonged QRS complex or an AV block.

### **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, such as cranial malformations and encephalocele, 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**

Lactose Monohydrate  
Pre-gelatinised Starch  
Silica colloidal anhydrous  
Magnesium Stearate

*Coat (Opadry White):*

Hypromellose – E464  
Titanium dioxide – E171  
Macrogol – E1521)

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

24 months.

### **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

### **6.5 Nature and contents of container**

High density polyethylene bottles with a child-resistant closure, containing 100 or 500 film-coated tablets.  
PVC/PVDC blister strips with aluminium foil backing, containing 25 film-coated tablets.

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal**

No special requirements.

**7 MARKETING AUTHORISATION HOLDER**

Chanelle Medical Unlimited Company  
Dublin Road  
Loughrea  
Co. Galway  
H62 FH90  
Ireland

**8 MARKETING AUTHORISATION NUMBER**

PA0688/063/001

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 25<sup>th</sup> October 2019

**10 DATE OF REVISION OF THE TEXT**

January 2023