Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nortriptyline 10 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains nortriptyline hydrochloride equivalent to 10 mg nortriptyline

Excipient(s) with known effect: Lactose monohydrate
Each tablet contains 26.80 mg lactose monohydrate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated Tablet
The 10 mg tablets are white, round shaped, film-coated tablets debossed “10” on one side with diameter of 5.55 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Nortriptyline is indicated for the relief of symptoms of depression.

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 (50mg once daily or 25mg 2-3 times daily). If necessary, dose could be gradually increased in 25mg increments no more than rapidly than every other day to be added to the morning dose. When doses above 100mg daily are administered, monitoring of plasma levels of nortriptyline should be considered 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.

Plasma levels
The dosage should be started at a low level and gradually increased, with the clinical response and any evidence of intolerance is closely monitored. The optimal therapeutic plasma concentration of nortriptyline is located at 50 - 150 ng / ml.

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
Special populations

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.

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.

Paediatric population
The use of nortriptyline in children and adolescents is not recommended due to the lack of data on safety and efficacy (see section 4.4).

Renal impairment
Impaired renal function in patients with renal impairment should be titrated carefully. In most cases, nortriptyline can be given at the usual doses.

Hepatic impairment
A lower or less frequent dose should be considered in patients with hepatic impairment, concurrent diseases, or who are taking multiple medications (see sections 4.4 Special Warnings and Precautions for Use and 4.5 interactions with other Medicinal products and other forms of Interaction").

Duration of treatment
The antidepressive effect usually sets in after 2-4 weeks. Treatment with antidepressants is symptomatic and should therefore be continued for a sufficient period of time, usually 6 months or longer to prevent recurrence.

Discontinuation
Treatment should be discontinued gradually, otherwise withdrawal symptoms such as headache, sleep disturbances, irritability and malaise could develop. These symptoms are not indicative of addiction.

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, coronary artery disease, any degree of heart block or other cardiac arrhythmias.
- - As for all tricyclic antidepressants, nortriptyline should not be administered to patients who are treated with monoamine oxidase inhibitors (MAOi, e.g., phenelzine, tranylcypromine, etc.). Concomitant use of nortriptyline and a MAOi might cause serotonin syndrome (a syndrome that can include symptoms such as agitation, confusion, tremor, myoclonia and hyperthermia). Nortriptyline therapy can begin 14 days after the termination of a MAOi, and 1 day after the termination of the reversible MAOi moclobemide. Treatment with MAOIs can begin 14 days after the terminations of treatment with nortriptyline (see section 4.5).

4.4 Special warnings and precautions for use

Paediatric population
Nortriptyline should not be used in the treatment of depression in children and adolescents under the age of 18 years. Studies in depression of this age group did not show a beneficial effect for class of tricyclic antidepressants. 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 sections 4.8 and 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.

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.

Cardiac arrhythmias are likely to occur with high dosage. They may also occur in patients with preexisting heart disease taking normal dosage.

Unmasking of Brugada syndrome has been reported in patients treated with nortriptyline. Brugada syndrome is a rare hereditary disease of the cardiac sodium channel with characteristic ECG changes (ST segment elevation and T wave abnormalities in the right precordial leads), which may lead to cardiac arrest and/or sudden death. Nortriptyline should generally be avoided in patients with Brugada syndrome or those suspected of having Brugada syndrome. Caution is advised in patient with risk factors such as a family history of cardiac arrest or sudden death (see sections 4.8 and 4.9).

Withdrawal symptoms, including insomnia, irritability, nausea, headache 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.

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.
If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy with buprenorphine should be considered depending on the severity of the symptoms.

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

Patients with cardiovascular disease or hypotension 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. Arrhythmias and hypotension can occur in patients without prior risk, especially when high doses are prescribed. Therefore patients who receive high doses should be followed up for arrhythmias and hypotension.

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

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

The elderly are particularly liable to experience adverse reactions, especially agitation, confusion, other anti-cholinergic reactions 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, raised intra-ocular pressure or symptoms suggestive of urinary retention or 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 (250 mg/day), after the addition of nortriptyline (125 mg/day).
Adjustment of anti-diabetic therapy may, therefore, be necessary.

In patients developing throat pain, fever and flu symptoms during the first 10 weeks of treatment, it is recommended that a FBC is taken to exclude agranulocytosis.

Hyperpyrexia has been reported during treatment with tricyclic antidepressants together with anticholinergic or with neuroleptics, especially during hot weather.

The tablets contain lactose monohydrate. Patients with rare hereditaty problems of galactose intolerance, total lactose deficiency or glucose-galactose malabsorbtion 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, 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.

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).

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 (e.g., quinidine), should be approached with caution.

The combination of nortriptyline with medications that increase the QT interval: such as quinidine, antihistamines such as astemizole and terfenadine, some antipsychotics (mainly pimozide and sertindole), cisaptide, halofrantine, and sotalol can increase the risk for ventricular arrhythmias in combination with Tricyclic antidepressants (TCA). TCAs have some characteristics of class I anti-arrhythmics. Caution is warranted in combination with anti-arrhythmics from this class, with beta-receptor blockers and with calcium antagonists (especially verapamil) due to a potentiating effect on the AV-conduction time and negative inotropic effects. In combination with class I anti-arrhythmias and loop and thiazide diuretics attention should be paid to potential inhibitory effect on the QT time due to potassium loss.

Antifungal medication such as fluconazole and terbinafine increase the serum concentration of tricyclic antidepressants and the associated toxicity. Syncope and Torsade de Pointes have been reported.

In combination with levothyroxine antidepressants can give rise to hyperthyroidism and Levothyroxine may strengthen the antidepressant effect.

The metabolism of levodopa in the intestine may be accelerated, possibly through delay of peristalsis.

TCAs may increase the risk of seizure in patients using tramadol.

The "serotonin syndrome" (changes in cognition, behaviour, function of the autonomic nervous system and neuromuscular activity) have been reported when nortriptyline is administered together with serotonin enhancing medications.

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

Supervision and adjustment of dosage may be required when nortriptyline is used with other anticholinergic drugs due to an increased risk of paralytic ileus, delirium and hyperpyrexia.

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 indicate no malformative or feto/neonatal toxicity. 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 2nd and 3rd 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, hypertonism, 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.

4.7 Effects on ability to drive and use machines

Nortriptyline is not a particularly sedating drug. Patients treated with psychotropic drugs can expect a deterioration in vigilance and attention and should be warned of the potential risk that their ability to drive or use machinery.

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.

Adverse reactions listed below are classified according to frequency and System Organ Class (SOC). Frequency categories are defined according to the following convention:

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)

SOC/frequency	**Adverse reaction**
Blood and lymphatic system disorders	
Rare:	Bone marrow depression, agranulocytosis, leucopenia, eosinophilia, thrombocytopenia
Endocrine disorders	
Not known:	SIADH
Metabolism and nutrition disorders	
Rare:	Decreased appetite, weight gain or loss
Not known:	Hyponatraemia
Psychiatric disorders	
Common:	Confusion, decreased libido
Uncommon:	Hypomania, mania, anxiety, insomnia, changes in sleep pattern including nightmares
Rare:	Delirium / confusional state (especially in older patients), hallucinations (in schizophrenic patients), irritability
Not known:	Suicidal ideation and suicidal behaviours have been reported during nortriptyline therapy or early treatment discontinuation (see Section 4.4). Agitation, restlessness, aggressive outbursts, delusions, orgasm disorders in women, increased libido, disorientation.
Nervous system disorders	
Very common:	Tremor, dizziness, headache
Common:	Concentration disorders, taste disorders, paraesthesia, ataxia, strange body movements.
Uncommon:	Seizures, numbness
Rare:	Clumsiness
Very rare:	Alterations in brain function (including perhaps seizures)
Eye disorders	
Very common:	Accommodation disorder including blurred vision
Common:	Mydriasis
Ear and labyrinth disorders	
Uncommon:	Tinnitus
Cardiacdisorders	
Very common:	Palpitation, irregular or heavy heart beats and tachycardia
Common:	Atrioventricular block, bundle branch block, high or low blood pressure
Rare:	Arrhythmias
Very rare:	Peripheral oedema
Not known:	Brugada Syndrome (unmasking) (frequency unknown)
Vascular disorders	
Very common:	Orthostatic hypotension
Uncommon:	Hypertension
Gastrointestinal disorders	
Very common:	Dry mouth, constipation, nausea
Uncommon:	Diarrhoea, vomiting, tongue oedema
Rare:	Salivary gland enlargement , paralytic ileus, loss of appetite, diarrhoea and stomach cramps

Hepatobiliary disorders	
Rare:	Jaundice
Not known:	Cholestasis
Skin and subcutaneous disorders	
Very common:	Sweating, flushing
Uncommon:	Rash, urticaria, facial oedema
Rare:	Alopecia, photosensitivity
Renal and urinary disorders	
Uncommon:	Urinary retention, problems urinating (increased or decreased)
Reproductive system and breast disorders	
Common:	Erection dysfunction
Rare:	Gynaecomastia, changes in sexual performance
Very rare:	Galactorrhoea, swelling of testicles
General disorders and administration site conditions	
Common:	Fatigue, weakness
Rare:	Fever, peculiar taste, mouth or gum problems
Investigations	
Common:	Weight gain, abnormal ECG, QT prolongation, QRS complex prolongation
Uncommon:	Increased intraocular pressure
Rare:	Weight loss, abnormal liver function, increased blood alkaline phosphatase, increased transaminase
Very rare:	Changes in blood sugar levels
Class effects	Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and TCAs. The mechanism leading to this risk is unknown.

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

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: HPRA Pharmacovigilance. Website: 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.

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 100 msec is predictive of more severe toxicity. The absence of sinus tachycardia does not ensure a benign course. Hypotension may be caused by vasodilatation, central and peripheral alpha-adrenergic blockade and cardiac depression. In a healthy young person, prolonged resuscitation may be effective; one patient survived 5 hours of cardiac massage.

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

Treatment: Symptomatic and supportive therapy is recommended. 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 (100-200 mmol). 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 or agitation 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 of 50 mg (especially in children) may lead to clinically significant symptoms.
Cardiotoxicity and convulsions are more common in children and toxicological advice is recommended in all cases.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

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). The mean oral bioavailability is 51% (Fabs = 0.51 ± 0.05; range 0.46 - 0.59).

Distribution
The apparent volume of distribution (Vd)β, estimated after intravenous administration is 1633 ± 268 l; range 1460 to 2030 (21 ± 4 l/kg). Plasma protein binding is approximately 93%.
Nortriptyline crosses the placental barrier.

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

Elimination
The elimination half-life (t ½ 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/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

Malformations have been observed in animal reproduction studies, in particular cranial malformations and encephalocele.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Maize Starch
Microcrystalline Cellulose
Magnesium Stearate

Coating:
Hypromellose E6
Titanium Dioxide
Macrogol 6000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

High density polyethylene containers containing 100 and 500 tablets.
Alu-PVC/PVDC blisters in packs of 100 tablets. Each blister contains 10 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Pharmafile Limited
Medici House, Ashbourne Ind. Est
Ashbourne
Co. Meath

Ireland

8 MARKETING AUTHORISATION NUMBER

PA0599/005/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11th March 2016
Date of last renewal: 01st February 2021

10 DATE OF REVISION OF THE TEXT

March 2024