Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Aniva 50 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains amitriptyline hydrochloride equivalent to 50 mg amitriptyline.

Excipient with known effect
Each film-coated tablet contains 285 mg lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Round (10.1 mm in diameter), reddish brown, convex film-coated tablet, debossed with '50' on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Amitriptyline is indicated for:

- the treatment of major depressive disorder in adults
- the treatment of neuropathic pain in adults
- the prophylactic treatment of chronic tension type headache (CTTH) in adults
- the prophylactic treatment of migraine in adults
- the treatment of nocturnal enuresis in children aged 6 years and above when organic pathology, including spina bifida and related disorders, have been excluded and no response has been achieved to all other non-drug and drug treatments, including antispasmodics and vasopressin-related products. This medicinal product should only be prescribed by a healthcare professional with expertise in the management of persistent enuresis.

4.2 Posology and method of administration

Posology
Not all dosage schemes can be achieved with all the pharmaceutical forms/strengths. The appropriate formulation/strength should be selected for the starting doses and any subsequent dose increments.

Major depressive disorder
Dosage should be initiated at a low level and increased gradually, noting carefully the clinical response and any evidence of intolerability.

Adults
Initially 25 mg 2 times daily (50 mg daily). If necessary, the dose can be increased by 25 mg every other day up to 150 mg daily divided into two doses.

The maintenance dose is the lowest effective dose.

Elderly patients over 65 years of age and patients with cardiovascular disease
Initially 10 mg - 25 mg daily.

The daily dose may be increased up to 100 mg - 150 mg, depending on individual patient response and tolerability.

Daily doses above 100 mg should be used with caution.

The maintenance dose is the lowest effective dose.

Paediatric population
Amitriptyline 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.

Neuropathic pain, prophylactic treatment of chronic tension type headache and prophylactic treatment of migraine
Patients should be individually titrated to the dose that provides adequate analgesia with tolerable adverse drug reactions. Generally, the lowest effective dose should be used for the shortest duration required to treat the symptoms.

Adults
Recommended doses are 25 mg - 75 mg daily in the evening. Doses above 100 mg should be used with caution.

The initial dose should be 10 mg - 25 mg in the evening. Doses can be increased with 10 mg - 25 mg every 3 – 7 days as tolerated.

The dose can be taken once daily, or be divided into two doses. A single dose above 75 mg is not recommended.

The analgesic effect is normally seen after 2 - 4 weeks of dosing.

Elderly patients over 65 years of age and patients with cardiovascular disease

A starting dose of 10 mg - 25 mg in the evening is recommended.

Doses above 75 mg should be used with caution.
It is generally recommended to initiate treatment in the lower dose range as recommended for adults. The dose may be increased depending on individual patient response and tolerability.

Paediatric population
Amitriptyline should not be used in children and adolescents aged less than 18 years, as long term safety and efficacy have not been established (see section 4.4).

Duration of treatment

Neuropathic pain
Treatment is symptomatic and should therefore be continued for an appropriate length of time. In many patients, therapy may be needed for several years. Regular reassessment is recommended to confirm that continuation of the treatment remains appropriate for the patient.

Prophylactic treatment of chronic tension type headache and prophylactic treatment of migraine in adults
Treatment must be continued for an appropriate length of time. Regular reassessment is recommended to confirm that continuation of the treatment remains appropriate for the patient.

Nocturnal enuresis

Paediatric population
The recommended doses for:

- children aged 6 to 10 years: 10 mg - 20 mg. A more suitable dosage form should be used for this age group.
- children aged 11 years and above: 25 mg – 50 mg daily

The dose should be increased gradually.

Dose to be administered 1-1½ hours before bedtime.

An ECG should be performed prior to initiating therapy with amitriptyline to exclude long QT syndrome.

Duration of treatment
The maximum period of treatment course should not exceed 3 months.

If repeated courses of amitriptyline are needed, a medical review should be conducted every 3 months.

When stopping treatment, amitriptyline should be withdrawn gradually.

Special populations

Reduced renal function
This medicinal product can be given in usual doses to patients with renal failure.

Reduced liver function
Careful dosing and, if possible, a serum level determination is advisable.

Cytochrome P450 inhibitors of CYP2D6
Depending on individual patient response, a lower dose of amitriptyline should be considered if a strong CYP2D6 inhibitor (e.g. bupropion, quinidine, fluoxetine, paroxetine) is added to amitriptyline treatment (see section 4.5).

Known poor metabolisers of CYP2D6 or CYP2C19
These patients may have higher plasma concentrations of amitriptyline and its active metabolite nortriptyline. Consider a 50% reduction of the recommended starting dose.

Method of administration
Amitriptyline is for oral use.
The tablets should be swallowed with water.

Discontinuation of treatment
When stopping therapy the drug should be gradually withdrawn over several weeks.

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 disorders of cardiac rhythm and coronary artery insufficiency.

Concomitant treatment with MAOIs (monoamine oxidase inhibitors) is contra-indicated (see section 4.5).
Simultaneous administration of amitriptyline and MAOIs may cause serotonin syndrome (a combination of symptoms, possibly including agitation, confusion, tremor, myoclonus and hyperthermia).

Treatment with amitriptyline 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 amitriptyline.

Severe liver disease.

In children under 6 years of age.

4.4 Special warnings and precautions for use

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.

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 proarrythmic risk.

Anaesthetics given during tri/tetracyclic 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.

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

Elderly patients are particularly susceptible to orthostatic hypotension.

This medical product should be used with caution in patients with convulsive disorders, urinary retention, prostatic hypertrophy, hyperthyroidism, paranoid symptomatology and advanced hepatic or cardiovascular disease, pylorus stenosis and paralytic ileus.

In patients with the rare condition of shallow anterior chamber and narrow chamber angle, attacks of acute glaucoma due to dilation of the pupil may be provoked.

Suicide/suicidal thoughts

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.

In manic-depressives, a shift towards the manic phase may occur; should the patient enter a manic phase amitriptyline should be discontinued.

As described for other psychotropics, amitriptyline may modify insulin and glucose responses calling for adjustment of the antidiabetic therapy in diabetic patients; in addition the depressive illness itself may affect patients' glucose balance.

Hyperpyrexia has been reported with tricyclic antidepressants when administered with anticholinergic or with neuroleptic medications, especially in hot weather.

After prolonged administration, abrupt cessation of therapy may produce withdrawal symptoms such as headache, malaise, insomnia and irritability.

Amitriptyline should be used with caution in patients receiving SSRIs (see sections 4.2 and 4.5).

Nocturnal enuresis

An ECG should be performed prior to initiating therapy with amitriptyline to exclude long QT syndrome.

Amitriptyline for enuresis should not be combined with an anticholinergic drug. Suicidal thoughts and behaviours may also develop during early treatment with antidepressants for disorders other than depression; the same precautions observed when treating patients with depression should therefore be followed when treating patients with enuresis.

Paediatric population

Long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are not available (see section 4.2).

Excipients
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Potential for amitriptyline to affect other medicinal products

Contraindicated combinations
MAOIs (non-selective as well as selective A (moclobemide) and B (selegiline))- risk of "serotonin syndrome" (see section 4.3).

Concomitant treatment with MAOIs (monoamine oxidase inhibitors) is contra-indicated.
Simultaneous administration of amitriptyline and MAOIs may cause serotonin syndrome (a combination of symptoms, possibly including agitation, confusion, tremor, myoclonus and hyperthermia).

Treatment with amitriptyline 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 amitriptyline.

Combinations that are not recommended
Sympathomimetic agents: Amitriptyline may potentiate the cardiovascular effects of adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine, and phenylpropanolamine (e.g. as contained in local and general anaesthetics and nasal decongestants).

Adrenergic neurone blockers: Tricyclic antidepressants may counteract the antihypertensive effects of centrally acting antihypertensives such as guanethidine, betanidine, reserpine, clonidine and methyldopa. It is advisable to review all antihypertensive therapy during treatment with tricyclic antidepressants.

Anticholinergic agents: Tricyclic antidepressants may potentiate the effects of these drugs 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 amitriptyline 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 amitriptyline and diuretics inducing hypokalaemia (e.g. furosemide).

Thioridazine: Co-administration of amitriptyline 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 amitriptyline increases the risk for seizures and serotonin syndrome. Additionally, this combination can inhibit the metabolism of tramadol to the active metabolite and thereby increasing tramadol concentrations potentially causing opioid toxicity.

Antifungals such as fluconazole and terbinafine increase serum concentrations of tricyclics and accompanying toxicity. Syncope and torsade de pointes have occurred.

Combinations requiring precautions for use
CNS depressants: Amitriptyline may enhance the sedative effects of alcohol, barbiturates, and other CNS depressants.

Potential of other medicinal products to affect amitriptyline

Tricyclic antidepressants (TCA) including amitriptyline are primarily metabolised by the hepatic cytochrome P450 isozymes CYP2D6 and CYP2C19, which are polymorphic in the population. Other isozymes involved in the metabolism of amitriptyline are CYP3A4, CYP1A2 and CYP2C9.

CYP2D6 inhibitors: The CYP2D6 isozyme can be inhibited by a variety of drugs, 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 to monitor TCA plasma levels, whenever a TCA is to be co-administered with another drug known to be an inhibitor of CYP2D6. Dose adjustment of amitriptyline 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. Antifungals such as fluconazole (CYP2C9 inhibitor) and terbinafine (CYP2D6 inhibitor) have been observed to increase serum levels of amitriptyline and nortriptyline.

The CYP3A4 and CYP1A2 isozymes metabolise amitriptyline to a lesser extent. However, fluvoxamine (strong CYP1A2 inhibitor) was shown to increase amitriptyline plasma concentrations and this combination should be avoided. Clinically relevant interactions may be expected with concomitant use of amitriptyline and strong CYP3A4 inhibitors such as ketoconazole, itraconazole and ritonavir.

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 amitriptyline free plasma concentrations and nortriptyline concentrations were increased.

Amitriptyline plasma concentration can be increased by sodium valproate and valpromide.
Clinical monitoring is therefore recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy
For amitriptyline only limited clinical data are available regarding exposed pregnancies.

Animal studies have shown reproductive toxicity (see section 5.3).
Amitriptyline is not recommended during pregnancy unless clearly necessary and only after careful consideration of the risk/benefit.

During chronic use and after administration in the final weeks of pregnancy, neonatal withdrawal symptoms can occur. This may include irritability, hypertonia , tremor, irregular breathing, poor drinking and loud crying and possibly anticholinergic symptoms (urinary retention, constipation).

Breast-feeding
Amitriptyline and its metabolites are excreted into breast milk (corresponding to 0.6 % - 1 % of the maternal dose). A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from the therapy of this medicinal product taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility
Amitriptyline reduced the pregnancy rate in rats (see section 5.3).
No data on the effects of amitriptyline on human fertility are available.

4.7 Effects on ability to drive and use machines

Amitriptyline is a sedative drug.

Patients who are prescribed psychotropic medication may be expected to have some impairment in general attention and concentration and should be cautioned about their ability to drive or operate machinery. These adverse effects can be potentiated by the concomitant intake of alcohol.

4.8 Undesirable effects

Amitriptyline may induce side effects similar to other tricyclic antidepressants. Some of the below mentioned side effects e.g. headache, tremor, disturbance in attention, constipation and decreased libido may also be symptoms of depression and usually attenuate when the depressive state improves.

In the listing below the following convention is used:

MedDRA system organ class / preferred term;
Very common (> 1/10);
Common (> 1/100, < 1/10);
Uncommon (> 1/1,000, < 1/100);
Rare (> 1/10,000, < 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.
Metabolism and nutrition disorders	Rare	Decreased appetite
	Not known	Anorexia, elevation or lowering 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) , suicidal thoughts or behaviour*.
	Not known	Paranoia.
Nervous system disorders	Very common	Somnolence, tremor, dizziness, headache, drowsiness, speech disorder (dysarthria).
	Common	Disturbance in attention, dysgeusia. paresthesia, ataxia.
	Uncommon	Convulsion.
	Very rare	Akathisia, polyneuropathy.
	Not known	Extrapyramidal disorder.
Eye disorders	Very common	Accommodation disorder.
	Common	Mydriasis.
	Very rare	Acute glaucoma.
	Not known	Dry eye.
Ear and labyrinth disorders	Uncommon	Tinnitus.
Cardiac disorders	Very common	Palpitations, tachycardia
	common	Atrioventricular block, bundle branch block.
	Unknown	Collapse conditions, worsening of cardiac failure
	Rare	Arrhythmia.
	Very rare	Cardiomyopathies, torsades de pointes.
	Not known	Hypersensitivity myocarditis.
Vascular disorders	Very 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	Rare	Jaundice.
	Uncommon	Hepatic impairment (e.g. cholestatic liver disease).
	Not known	Hepatitis.
Skin and subcutaneous tissue disorders	Very common	Hyperhidrosis.
	Uncommon	Rash, urticaria, face oedema.
	Rare	Alopecia, photosensitivity reaction.
Renal and urinary disorders	Common	Micturition disorders.
	Uncommon	Urinary retention.
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 increased.
	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.

*Case reports of suicidal thoughts or behaviour were reported during the treatment with or just after conclusion of the treatment with amitriptyline (see section 4.4).

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.

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

Symptoms
Anticholinergic symptoms: Mydriasis, tachycardia, urinary retention, dry mucous membranes, reduced bowel motility. Convulsions. Fever. Sudden occurrence of CNS depression. Lowered consciousness progressing into coma. Respiratory depression. Hyperreflexia may be present with extensor plantar reflexes. Hypothermia may occur.

Cardiac symptoms: Arrhythmias (ventricular tachyarrhythmias, torsade de pointes, ventricular fibrillation). The ECG characteristically show 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 standstill. Widening of the QRS-complex usually correlates well with the severity of the toxicity following acute overdoses. Heart failure, hypotension, cardiogenic shock. Metabolic acidosis, hypokalemia, hyponatraemia.

Ingestion of 750 mg or more by an adult may result in severe toxicity. The effects in overdose will be potentiated by simultaneous ingestion of alcohol and other psychotropic. There is considerably individual variability in response to overdose. Children are especially susceptible to cardiotoxicity, seizures and hyponatraemia.

During awakening possibly again confusion, agitation and hallucinations and ataxia.

Treatment

1. Admission to hospital (intensive care unit) if required. Treatment is symptomatic and supportive.
2. Assess and treat ABC's (airway, breathing and circulation) as appropriate. Secure an IV access. Close monitoring even in apparently uncomplicated cases.
3. Examine for clinical features. Check urea and electrolytes—look for low potassium and monitor urine output. Check arterial blood gases—look for acidosis. Perform electrocardiograph—look for QRS>0.16 seconds

4. Do not give flumazenil to reverse benzodiazepine toxicity in mixed overdoses.
5. Consider gastric lavage only if within one hour of a potentially fatal overdose.
6. Give 50 g of charcoal if within one hour of ingestion.
7. Patency of the airway is maintained by intubation, where required. Treatment in respirator is advised to prevent a possible respiratory arrest. Continuous ECG-monitoring of cardiac function for 3-5 days. Treatment of the following will be decided on a case by case basis:- Wide QRS-intervals, cardiac failure and ventricular arrhythmias- Circulatory failure- Hypotension- Hyperthermia- Convulsions- Metabolic acidosis.
8. Unrest and convulsions may be treated with diazepam.
9. Patients who display signs of toxicity should be monitored for a minimum of 12 hours.
10. Monitor for rhabdomyolysis if the patient has been unconscious for a considerable time.
11. Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase. Deaths by deliberate or accidental overdosage have occurred with this class of medicament.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidepressants - Non-selective monoamine reuptake inhibitor (tricyclic antidepressant), ATC code: N06AA09

Mechanism of action

Amitriptyline is a tricyclic antidepressant and an analgesic. It has marked anticholinergic and sedative properties. It prevents the re-uptake, and hence the inactivation of noradrenaline and serotonin at nerve terminals. Reuptake prevention of these monoamine neurotransmitters potentiate their action in the brain. This appears to be associated with the antidepressant activity.

The mechanism of action also includes ion-channel blocking effects on sodium, potassium and NMDA channel at both central and spinal cord level. The noradrenaline, sodium and the NMDA effects are mechanisms known to be involved in the maintenance of neuropathic pain, chronic tension type headache prophylaxis and migraine prophylaxis. The pain reducing effect of amitriptyline is not linked to its anti- depressive properties.

Tricyclic antidepressants possess affinity for muscarinic and histamine H1 receptors to varying degrees

Clinical efficacy and safety

The efficacy and safety of amitriptyline has been demonstrated in treatments of the following indications in adults:

- Major Depressive Disorder
- Neuropathic Pain
- Chronic tension type headache prophylaxis
- Migraine prophylaxis

The efficacy and safety of amitriptyline has been demonstrated for treatments of nocturnal enuresis in children aged 6 years and above (see section 4.1).
The recommended doses are provided in section 4.2. For treatment of depression, doses of up to 200 mg daily and, occasionally, up to 300 mg daily have been used in severely depressed patients in hospital.

The antidepressant and analgesic effects usually set in after 2-4 weeks; the sedative action is not delayed.

5.2 Pharmacokinetic properties

Absorption

Film-coated tablets

Oral administration of tablets results in maximum serum levels in about 4 hours.
(t_{max}= 3.89±1.87 hours; range 1.93-7.98 hours). After peroral administration of 50 mg the mean C_{max}= 30.95±9.61 ng/ml; range 10.85-45.70 ng/ml (111.57±34.64 nmol/l; range 39.06-164.52 nmol/l). The mean absolute oral bioavailability is 53% (F_{abs}= 0.527±0.123; range 0.219-0.756).

Distribution

The apparent volume of distribution $(Vd)_\beta$ estimated after intravenous administration is 1221 L ± 280 L; range 769-1702 L (16 ± 3 L/kg).

The plasma protein binding is about 95%.

Amitriptyline and the main metabolite nortriptyline pass across the placental barrier.

In nursing mothers amitriptyline and nortriptyline are excreted in small amounts with the breast milk. The ratio milk concentration/plasma concentration in women is around 1:1. The estimated daily infant exposure (amitriptyline + nortriptyline) averages 2% of the corresponding maternal weight related doses of amitriptyline (in mg/kg) (see section 4.6).

Biotransformation
In vitro the metabolism of amitriptyline proceeds mainly by demethylation (CYP2C19, CYP3A4) and hydroxylation (CYP2D6) followed by conjugation with glucuronic acid. Other isozymes involved are CYP1A2 and CYP2C9. The metabolism is subject to genetic polymorphism. The main active metabolite is the secondary amine, nortriptyline.

Nortriptyline is a more potent inhibitor of noradrenaline than of serotonin uptake, while amitriptyline inhibits the uptake of noradrenaline and serotonin equally well. Other metabolites such as cis- and trans-10-hydroxyamitriptyline and cis- and trans-10-hydroxynortriptyline have the same profile as nortriptyline but is considerably weaker. Demethylnortriptyline and amitriptyline N oxide are only present in plasma in minute amounts; the latter is almost inactive. All the metabolites are less anticholinergic than amitriptyline and nortriptyline. In plasma the amount of total 10-hydroxynortriptyline dominates but most of the metabolites are conjugated.

Elimination
The elimination half-life ($t_{½\beta}$) amitriptyline after peroral administration is about 25 hours (24.65 ± 6.31 hours; range 16.49-40.36 hours). The mean systemic clearance (Cls) is 39.24 ± 10.18 L/h, range 24.53-53.73 L/h.

The excretion proceeds mainly with urine. The renal elimination of unchanged amitriptyline is insignificant (about 2%).

Steady state plasma levels of amitriptyline + nortriptyline are reached within a week for most patients, and in steady state the plasma level comprises approximately equal parts of amitriptyline and nortriptyline around the clock following treatment with conventional tablets 3 times a day.

Elderly patients
Longer half-lives and decreased oral (Cl_o) clearance values due to a reduced rate of metabolism have been demonstrated in elderly patients.

Reduced hepatic function
Hepatic impairment may reduce hepatic extraction resulting in higher plasma levels and caution should be exercised when dosing these patients (see section 4.2).

Reduced renal function
Renal failure has no influence on the kinetics.

Polymorphism
The metabolism is subject to genetic polymorphism (CYP2D6 and CYP2C19) (see section 4.2).

Pharmacokinetic/pharmacodynamic relationship
Plasma concentrations of amitriptyline and nortriptyline vary very widely between individuals and no simple correlation with therapeutic response has been established.
The therapeutic plasma concentration in major depression is around 80 – 200 ng/ml (≈ 280 – 700 nmol/l) (for amitriptyline + nortriptyline). Levels above 300-400 ng/ml are associated with increased risk of disturbance in cardiac conduction in terms of prolonged QRS-complex or AV block.

5.3 Preclinical safety data

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

The genotoxic potential of amitriptyline has been investigated in various in vitro and in vivo studies. Although these investigations revealed partially contradictory results, a particularl potential to induce chromosomal aberrations cannot be excluded. Long-term carcinogenicity studies have not been performed.

In reproductive studies teratogenic effects were not observed in mice, rats, or rabbits when amitriptyline was given orally at doses of 2-40 mg/kg/day (up to 13 times the maximum recommended human amitriptyline dose of 150 mg/day or 3 mg/kg/day for a 50-kg patient). However, literature data have suggested a risk for malformations and delays in ossification of mice, hamsters, rats and rabbits at 9-33 times the maximum recommended dose. There was a possible association with an effect on fertility in rats, namely a lower pregnancy rate. The reason for this effect on fertility is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose
Maize starch
Copovidone
Sodium starch glycolate
Talc
Magnesium stearate

Film-coating:
Hypromellose
Titanium dioxide (E 171)
Macrogol
Iron oxide red (E 172)
Iron oxide yellow (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVdC//Alu blisters containing 7, 10, 14, 20, 21, 28, 30, 50, 56, 60, 84, 90 or 100 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Azure Pharmaceuticals Ltd.
12 Hamilton Drive
The Rock Road
Blackrock

Co. Louth
A91 T997
Ireland

8 MARKETING AUTHORISATION NUMBER

PA22871/023/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28th February 2025

10 DATE OF REVISION OF THE TEXT