

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Amitriptyline 10 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg of Amitriptyline hydrochloride.

Excipients of known effect: Also contains lactose 49.0 mg per tablet.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Pale blue coloured, circular biconvex film-coated tablets with “BL” debossed on one side and “10” on the other 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 100mg – 150mg, divided into two doses, depending on individual patient response and tolerability.

Daily doses above 100mg 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 long term 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 prophylaxis

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 25mg - 75mg daily in the evening. Doses above 100mg should be taken 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 75mg 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 10mg - 25mg in the evening is recommended. Doses above 75mg should be used with caution.

It is generally recommended to initiate treatment in the lower dose range as recommended for adult. 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: 10mg - 20mg. A suitable dosage form should be used for this age group.
- children aged 11 years and above: 25mg – 50mg 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.

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 amitriptyline hydrochloride, tricyclic antidepressants 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 contraindicated (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.
- Prior sensitisation to amitriptyline.
- History of myocardial infarction, arrhythmias, particularly heart block of any degree; mania, congestive heart failure, coronary artery insufficiency
- Severe liver disease, porphyria
- Lactation (see section 4.6)

- 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 proarrhythmic 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).

Avoid if possible in patients with blood dyscrasias and a history of epilepsy.

When used for the depressive component of schizophrenia, amitriptyline should be used with caution as it may aggravate psychotic symptoms. Paranoid delusions, with or without associated hostility, may be aggravated. A major tranquilliser should be given concurrently in such cases, or dosage of amitriptyline reduced.

Unless essential, it is inadvisable to combine amitriptyline and electroconvulsive therapy (ECT).

Hyponatraemia (usually in the elderly and possibly due to inappropriate secretion of antidiuretic hormone) has been associated with all types of antidepressants and should be considered in all patients who develop drowsiness, confusion or convulsions while taking an antidepressant. (See section 4.8).

Serotonin syndrome

Concomitant administration of buprenorphine/naloxone and other serotonergic agents, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5).

If concomitant treatment with other serotonergic 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 should be considered depending on the severity of the symptoms.

Lactose

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

4.5 Interaction with other medicinal products and other forms of interaction

Contraindicated combinations

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

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 methyl dopa. It is advisable to review all antihypertensive therapy during treatment with tricyclic antidepressants. There is an increased risk of hypertension on clonidine withdrawal.

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 amiodarone (avoid concomitant use), disopyramide, procainamide, propafenone, quinidine, the antihistamines astemizole and terfenadine, some antipsychotics (notably pimozide, sertindole, thioridazine and clozapine), 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.

Buprenorphine-containing medicinal products:

Serotonergic medicinal products, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

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.

Alpha₂-adrenoceptor stimulants

Concomitant use of apraclonidine and brimonidine should be avoided.

Altretamine

Risk of severe postural hypotension.

Anaesthetics

Concomitant therapy may increase the risk of arrhythmias and hypotension. If surgery is necessary, the anaesthetist should be informed that a patient is being so treated (see section 4.4).

Analgesics

There is a possibility of increased side effects with nefopam. There is a possibility of increased sedation with opioid analgesics.

Antibacterials

Concomitant use with linezolid may result in CNS excitation and hypertension.

Anxiolytics and hypnotics

Concomitant use enhances the sedative effect. Caution is advised if patients receive large doses of ethchlorvynol concurrently. Transient delirium has been reported in patients treated with 1g ethchlorvynol and 75mg to 150mg of amitriptyline.

Disulfiram

Concomitant use may inhibit the metabolism of tricyclics. Delirium has been reported in patients taking amitriptyline with disulfiram.

Diuretics

Increased risk of postural hypotension.

Dopaminergics

Concomitant use with entacapone should be avoided. CNS toxicity has been reported with selegiline.

Muscle relaxants

Concomitant use of baclofen enhances its muscle relaxant effect.

Nitrates

Reduced effect of sublingual nitrates (owing to dry mouth).

Oestrogens and progestogens

Oral contraceptives antagonise the antidepressant effect but side-effects may be increased due to increased plasma concentrations of tricyclics.

Sibutramine

Concomitant use is not recommended due to the increased risk of CNS toxicity.

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 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.

Very Common ($\geq 1/10$), Common ($\geq 1/100 < 1/10$), Uncommon ($\geq 1/1000 < 1/100$), Rare ($\geq 1/10,000 < 1/1000$), Very Rare ($< 1/10,000$), Frequency not known (cannot be estimated from the available data).

MedDRA SOC	Frequency	Preferred term
Blood and lymphatic system disorders	Rare	Bone marrow depression, agranulocytosis, eosinophilia, leucopenia, thrombocytopenia and purpura

Metabolism and nutrition disorders	<i>Rare</i>	Decreased appetite
	<i>Frequency not known</i>	Elevation or lowering of blood sugar levels. Increased appetite. Anorexia.
Psychiatric disorders	<i>Very common</i>	Aggression.
	<i>Common</i>	Confusional states, libido decrease, agitation.
	<i>Uncommon</i>	Hypomania, mania, anxiety, insomnia, nightmares,
	<i>Rare</i>	Delirium (in elderly patients), hallucinations , suicidal thoughts or behaviour*.
	<i>Frequency not known</i>	Paranoia.
Nervous system disorders	<i>Very common</i>	Somnolence, tremors, dizziness, headache, drowsiness, speech disorders (dysarthria).
	<i>Common</i>	Disturbance in attention, dysgeusia, paraesthesia, ataxia.
	<i>Uncommon</i>	Convulsions.
	<i>Very Rare</i>	Akathisia, polyneuropathy.
	<i>Frequency not known</i>	weakness, disturbed concentration, disorientation, delusions, restlessness, peripheral neuropathy, inco-ordination, extrapyramidal effects.
Eye disorders	<i>Very common</i>	Accommodation disorder.
	<i>Common</i>	Mydriasis.
	<i>Very rare</i>	Acute glaucoma.
	<i>Frequency not known</i>	Blurred vision, Dry eye
Ear and labyrinth disorders	<i>Uncommon</i>	Tinnitus.
Cardiac disorders	<i>Very common</i>	Palpitations, tachycardia.
	<i>Common</i>	Atrioventricular block, bundle branch block.
	<i>Uncommon</i>	Collapse conditions, worsening of cardiac failure.
	<i>Rare</i>	Arrhythmias.
	<i>Very rare</i>	Cardiomyopathies, torsades de pointes.
	<i>Frequency not known</i>	Hypersensitivity myocarditis, myocardial infarction.
Vascular disorders	<i>Very common</i>	Orthostatic hypotension.
	<i>Uncommon</i>	Hypertension.
	<i>Frequency not known</i>	Hyperthermia, stroke.
Respiratory, thoracic, and	<i>Very common</i>	Congested nose.

mediastinal disorders	<i>Very rare</i>	Allergic inflammation of the pulmonary alveoli and of the lung tissue, respectively (alveolitis, Löffler's syndrome).
Gastrointestinal disorders	<i>Very common</i>	Dry mouth, constipation, nausea.
	<i>Uncommon</i>	Diarrhoea, vomiting, tongue oedema.
	<i>Rare</i>	Salivary gland enlargement, ileus paralytic.
	<i>Frequency not known</i>	Epigastric distress, stomatitis, black tongue.
Hepatobiliary disorders	<i>Rare</i>	Jaundice.
	<i>Uncommon</i>	Hepatic impairment (e.g. cholestatic liver disease).
	<i>Frequency not known</i>	Hepatitis.
Skin and subcutaneous tissue disorders	<i>Very common</i>	Hyperhidrosis.
	<i>Uncommon</i>	Rash, urticaria, face oedema.
	<i>Rare</i>	Alopecia, photosensitivity reaction.
Renal and urinary disorders	<i>Common</i>	Micturition disorders.
	<i>Uncommon</i>	Urinary retention.
Reproductive system and breast disorders	<i>Common</i>	Erectile dysfunction.
	<i>Uncommon</i>	Galactorrhoea.
	<i>Rare</i>	Gynaecomastia.
	<i>Frequency not known</i>	Breast enlargement, testicular swelling, libido fluctuations, interference with sexual function, syndrome of inappropriate ADH secretion.
General disorders and administration site conditions	<i>Common</i>	Fatigue, feeling thirst.
	<i>Rare</i>	Pyrexia.
Investigations	<i>Very common</i>	Weight increased.
	<i>Common</i>	Electrocardiogram abnormal, electrocardiogram QT prolonged, electrocardiogram QRS complex prolonged, hyponatremia.
	<i>Uncommon</i>	Intraocular pressure increased.
	<i>Rare</i>	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).

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 increased risk is unknown.

Abrupt withdrawal after prolonged administration has caused nausea, headache and malaise. Gradual withdrawal has been associated with transient symptoms such as dream and sleep disturbances, irritability and restlessness during the first two weeks of dosage reduction. These are not thought to be signs associated with addiction. Mania or hypomania have been reported rarely within 2-7 days of stopping therapy with tricyclic antidepressants.

Side-effects in enuresis

As dosages used in enuresis are low compared to those used for depression, side-effects are less frequent. The most common are drowsiness and anticholinergic effects. Infrequently, mild sweating and itching have been reported. Behavioural changes have been observed in children receiving tricyclics for treatment of enuresis.

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 the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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

ATC code : N06A A09 Pharmacotherapeutic Group: Tricyclic Antidepressants - Non-selective monoamine reuptake inhibitor (tricyclic antidepressant)

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

5.2 Pharmacokinetic properties

Absorption

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

Distribution

The apparent volume of distribution (V_d) β estimated after intravenous administration is 1221 L \pm 280 L; range 769-1702 L (16 \pm 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 ($t_{1/2}$) of amitriptyline after peroral administration is about 25 hours (24.65 ± 6.31 hours; range 16.49-40.36 hours). The mean systemic clearance (Cl_s) 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 ($\approx 280 - 700$ 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, particularly a potential to induce chromosome

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 suggested a risk for malformations and delays in ossification of mice, hamsters, rats and rabbits at 9 33 times the maximum recommended dose. There was a possible association with an effect on fertility in rats, namely a lower pregnancy rate. The reason for the effect on fertility is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Microcrystalline cellulose
Lactose monohydrate
Crospovidone
Maize starch
Colloidal anhydrous silica
Talc
Magnesium stearate

Film coat:

Hypromellose
Talc
Titanium dioxide (E171)
Macrogol 6000
Indigo Carmine Al Lake (E 132)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.

Store in the original package (blister) in order to protect from moisture and light.

6.5 Nature and contents of container

PVC /Aluminium foil blisters of 7, 10, 14, 21, 28, 30, 56, 60, 84, 90, 100, 110, 112, 120, 150,160 or 168 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

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United Kingdom

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PL 17907/ 0131

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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