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” embossed on one side and “10” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

• Symptoms of depression (especially where sedation is required).

• Nocturnal enuresis where organic pathology is excluded. Amitriptyline is indicated for the treatment of nocturnal enuresis in children aged 6 years and above when organic pathology has been excluded and no response has been achieved to all other non-drug and drug treatments (use only as third line therapy). Amitriptyline should only be prescribed by healthcare professional with expertise in the management of persistent enuresis

4.2 Posology and method of administration

Posology

Therapy should be started with a low dosage and increased gradually, according to the clinical response and any evidence of intolerance.

The usual dosage(s) are described below:

Depression

Adults: Initially 50-75 mg daily either in divided doses or as a single night time dose gradually increasing to 150 –200mg daily according to clinical response, the additional doses being given in the late afternoon and/or at bedtime.

The sedative effect is usually rapidly apparent; however the antidepressant effect may be apparent within three to four days or may take up to 30 days to develop adequately.

A maintenance dose of 50 -100 mg at night should be given to lessen the chances of relapse.

Child under 16 years not recommended for depression.

Elderly: 10-25 mg three times a day is recommended initially, and this should be increased slowly. 50 mg a day may be satisfactory in the elderly, who may not tolerate higher doses. The dosage may be taken as divided doses, or as a single dose, preferably in the evening or at bedtime.

Adolescents: 25-50mg daily in divided doses or as a single dose at night. Half the normal maintenance dose may be sufficient to produce a satisfactory clinical response.

Nocturnal enuresis

Enuresis: An ECG should be performed prior to initiating therapy with amitriptyline to exclude long QT syndrome. The dose should be increased gradually. The initial treatment course is for 3 month. If repeated courses of amitriptyline are needed, a medical review should be conducted every 3 months. When stopping treatment, amitriptyline should be withdrawn gradually.

Children: 11-16 years: 25-50 mg daily taken at night for not more than three months. 6-10 years: 10-20 mg daily taken at night for not more than three months. Child under 6 years is not recommended.

These tablets should be taken as instructed swallowed with a glass of water. Continue to take them for as long as your doctor tells you to as it may be dangerous to stop without their advice. You may not notice any improvement in your symptoms for up to 4 weeks after starting treatment.

Method of Administration

For oral use

4.3 Contraindications

• Hypersensitivity to amitriptyline hydrochloride, tricyclic antidepressants or to any of the excipients listed in section 6.1

• Co administration with monoamine oxidase inhibitors or who have taken them within the last 14 days

- 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

Amitriptyline should be used with caution in patients with a history of epilepsy, in patients with impaired liver function and phaeochromocytoma, because of its atropine-like action, in patients with a history of urinary retention, prostatic hypertrophy, blood dyscrasias, narrow-angle glaucoma or increased intra-ocular pressure. Inpatients with narrow-angle glaucoma, even average doses may precipitate an attack of glaucoma.

Patients with cardiovascular disorders, hyperthyroid patients and those receiving thyroid medication or anticholinergic agents should be closely supervised and the dosage of all medications carefully adjusted when amitriptyline is given concurrently (see section 4.5).

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.

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.

Elderly patients are particularly liable to experience adverse reactions especially agitation, confusion and postural hypotension. The initial dose should be increased with great caution under close supervision.

When amitriptyline is used for the depressive component of schizophrenia, psychotic symptoms may be aggravated. In manic depressives, a shift towards the manic phase may occur; paranoid delusions, with or without associated hostility, may be aggravated. In such cases, a major tranquilliser should be given concurrently or the dosage of amitriptyline reduced.

The risk of suicide remains during treatment of depressed patients and until significant remission occurs such patients require careful supervision.

Concurrent administration with ECT may increase the hazards of treatment and should be limited to patients for whom it is deemed essential.

If possible, discontinue amitriptyline several days before surgery. But if emergency surgery is unavoidable, the anaesthetist should be informed that the patient is being treated with amitriptyline because anaesthesia may increase the risk of hypotension and arrhythmias.

Behavioural changes have been observed in children receiving tricyclics for the treatment of enuresis.

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).

<u>Suicide/suicidal thoughts or clinical worsening</u>

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.

Other psychiatric conditions for which amitriptyline is prescribed can also be associated with an increased risk of suicide related events. In addition, these conditions may be comorbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

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.

This product contains the excipient, lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Antidepressants: The concurrent use of anti-depressants having various mechanisms of action should be undertaken only with due recognition of their possible potentiation and with a thorough knowledge of their pharmacology. Monoamine oxidase inhibitors can potentiate the effects of tricyclic anti-depressants such as amitriptyline, and hyperpyretic crises, severe convulsions, and fatalities have occurred. A minimum of 14 days should elapse between discontinuing a MAOI and starting amitriptyline, which should be introduced cautiously and dosage increased gradually. Concomitant use of reboxetine should be with caution. The plasma concentrations of some tricyclics are increased by SSRIs. Fluoxetine markedly inhibits Cytochrome P450 II D6, which is involved in the metabolism of a number of tricyclic antidepressants. Patients should be monitored for increased antidepressant plasma levels and toxicity when fluoxetine is used concurrently. Adjustment of the antidepressant dosage may be necessary.

Alcohol: Enhances the sedative effect.

Altretamine: there is a risk of severe postural hypotension when amitriptyline and altretamine are used concurrently.

Alpha2-adrenoceptor stimulants: Concomitant use of apraclonidine and brimonidine should be avoided.

Analgesics: Nefopam side effects may be increased; the risk of convulsions with tramadol may possibly be increased. There is a possibility of increased sedation with opioid analgesics. Levacetylmethadol should not be used concomitantly with amitriptyline due to the increased risk of ventricular arrhythmias.

Anaesthetics: Anaesthetics may increase the risk of arrhythmias and hypotension in patients taking amitriptyline (see section 4.4) If surgery is necessary, the anaesthetist should be informed that a patient is being so treated (see section 4.4).

Antiarrhythmics: There is an increased risk of ventricular arrhythmias with drugs which prolong the QT interval, including amiodarone (avoid concomitant use), disopyramide, procainamide, propafenone and quinidine.

Antibacterials: The plasma concentrations of some tricyclic antidepressants may be reduced by rifampicin, leading to a reduced antidepressant effect. Concomitant use with linezolid may result in CNS excitation and hypertension

Monoamine oxidase inhibitors (MAOIs): The concurrent use of antidepressants having varying modes of action should be made only with due recognition of their possible potentiation and a thorough knowledge of their respective pharmacologies.MAOIs can potentiate the effects of tricyclic antidepressants such as amitriptyline and hyperpyretic crises, severe convulsions and fatalities have occurred. A minimum of 14 days should elapse between discontinuing a MAOI and starting amitriptyline which should be introduced cautiously and dosage increased gradually. CNS excitation and hypertension have occurred with MAOIs.

Antiepileptics:
Concomitant use of antiepileptics may lower the convulsive threshold. Barbiturates and carbamazepine may decrease, and methylphenidate may increase, the antidepressant action of amitriptyline

Antifungals: Increased serum concentraions have occurred in patients also taking Fluconazole. Serious adverse effects have been reported due to increased amitriptyline plasma concentration.

Antihistamines: Antimuscarinic and sedative effects may be increased. Avoid concomitant use with terfenadine as the risk of ventricular arrhythmias may be increased

Based on the known metabolism of amitriptyline, the protease inhibitor, ritonavir, may increase the serum levels of amitriptyline. Therefore, careful monitoring of therapeutic and adverse effects is recommended when these drugs are administered concomitantly.

Antihypertensives: Amitriptyline may block the antihypertensive action of adrenergic neurone blockers (e.g.guanethidine, debrisoquine, betanidine) and possibly clonidine. There is an increased risk of hypertension on clonidine withdrawal. It would be advisable to review all antihypertensive therapy during treatment with tricyclic antidepressants.

Anticholinergic drugs: Amitriptyline for enuresis should not be combined with an anticholinergic drug.

Sympathomimetic Agents: Amitriptyline should not be given with sympathomimetic agents such as adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine and phenylpropanolamine due to hypertension and arrhythmias. Local anaesthetics with adrenaline appear to be safe. Methylphenidate may inhibit the metabolism of tricyclics and therefore increase the antidepressant action of amitriptyline.

Other CNS Depressants: Amitriptyline may enhance the response to alcohol, barbiturates and other CNS depressants. In turn, barbiturates may decrease and the antidepressant action of amitriptyline. 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 amitriptyline.

Disulfiram: Delirium has been reported in patients taking amitriptyline with disulfiram. Concomitant use may inhibit the metabolism of tricyclics. Increased plasma concentrations and increased disulfiram reaction has been reported in patients taking amitriptyline, alcohol and disulfiram concomitantly.

Antimuscarinics: Paralytic ileus, urinary retention or acute glaucoma may occur in patients taking tricyclic antidepressants in combination with drugs having an anticholinergic action, especially in elderly patients.

Antipsychotics: the risk of ventricular arrhythmias is increased (avoid concomitant use with pimozide or thioridazine); plasma concentrations of some tricyclics are increased. Antimuscarinic side effects may be increased with phenothiazines and possibly clozapine.

Antivirals: Based on the known metabolism of amitriptyline, the protease inhibitor, ritonavir, may increase the serum levels of amitriptyline. Therefore, careful monitoring of therapeutic and adverse effects is recommended when these drugs are administered concomitantly.

Ulcer-healing Drugs: Cimetidine is reported to reduce hepatic metabolism of certain tricyclic antidepressants when taken concurrently resulting in increased plasma concentration of amitriptyline.

Anxiolytics and hypnotics: Concomitant use enhances the sedative effect.

Beta-blockers: The risk of ventricular arrhythmias associated with sotalol is increased.

Calcium-channel Blockers: Diltiazem and verapamil may increase the plasma concentration of amitriptyline.

Diuretics: There is an increased risk of postural hypotension.

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

Muscle Relaxants: The muscle relaxant effect of baclofen may be enhanced by concomitant use.

Nitrates: The effect of sublingual nitrates may be reduced (owing to the effect of dry mouth).

Oestrogens and Progestogens: Oral contraceptives antagonise the antidepressant effect but side effects may be increased due to the increased plasma concentration of amitriptyline.

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

Thyroid preparations e.g. levothyroxine: the action of tricyclic antidepressants such as amitriptyline may be accelerated by the concurrent use of thyroid hormone medication (see section 4.4)

St.John's Wort: St.John's wort may decrease plasma levels of amitryptiline

Concurrent administration of amitriptyline with electroconvulsive therapy should be limited to patients for whom it is considered essential, as the hazards of each treatment may be increased.

4.6 Fertility, pregnancy and lactation

The safety of amitriptyline for use during pregnancy and lactation has not been established. It is advised not to take Amitriptyline during pregnancy, especially during the first and last trimester, unless there are compelling reasons and in these patients the benefits should be weighed against the possible hazards to the foetus, child or mother.

Clinical experience of the use of amitriptyline in pregnancy has been limited. There is evidence of harmful effect in pregnancy in animals, when given in exceptionally high doses. Withdrawal symptoms, including respiratory depression and agitation have been reported in neonates whose mothers had taken tricyclic antidepressants during the last trimester of pregnancy. Urinary retention in the neonate has also been associated with maternal use of amitriptyline.

Breast feeding mothers: Amitriptyline is detectable in breast milk. Because of the potential for serious adverse reactions in infants from amitriptyline, a decision should be made whether to discontinue nursing or discontinue the drug.

4.7 Effects on ability to drive and use machines

Amitriptyline may impair alertness in some patients and activities made hazardous by diminished alertness (e.g. driving a car or operating machinery) should be avoided.

4.8 Undesirable effects

Like other medicines, Amitriptyline film coated tablets may occasionally cause side-effects in some patients, particularly when you first start taking it. Not all of these side effects have been experienced with amitriptyline but some have occurred with other medicines belonging to the same group as amitriptyline.

The following undesirable effects have been observed and reported during treatment with Amitriptyline film coated tablets with the following frequencies;

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) including isolated reports.

Cardiocvascular disorders: hypotension, syncope, postural hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke, and non-specific ECG changes in AV conduction. Cardiac arrhythmias and severe hypotension are likely to occur with high dosage or in deliberate over dosage. They may also occur in patients with pre-existing heart disease taking normal dosage.

Nervous system disorders: Dizziness, fatigue, headache, weakness, confusional states, disturbed concentration, disorientation, delusions, hallucinations, hypomania, excitement, anxiety, restlessness, drowsiness, insomnia, nightmares, numbness, tingling and paraesthesia of the extremities, peripheral neuropathy, incoordination, ataxia, tremors, coma, convulsions, alteration of the EEG, extrapyramidal symptoms, including abnormal involuntary movements and tardive dyskinesia, dysarthria, and tinnitus.

Cases of suicidal ideation and suicidal behaviours have been reported during amitriptyline therapy or early after treatment discontinuation (see section 4.4).

Anticholinergic effects reported are dry mouth, blurred vision, mydriasis, disturbance of accommodation, increased intra-ocular pressure, constipation, paralytic ileus, hyperpyrexia, urinary retention, and urinary tract dilatation.

Immune system disorders: Allergic reactions are characterised by skin rash, urticaria, photosensitisation, and oedema of the face and tongue.

Blood and lymphatic disorders: bone marrow depression including agranulocytosis, leucopenia, eosinophilia, purpura, and thrombocytopenia.

Gastrointestinal disorders: nausea, epigastric distress, vomiting, anorexia, stomatitis, taste disturbance, diarrhoea, parotid swelling, black tongue, and rarely hepatitis (including altered liver function and jaundice).

Endocrine disorders: testicular swelling, gynaecomastia, breast enlargement, galactorrhoea, increased or decreased libido, impotence, interference with sexual function (e.g. delayed ejaculation, anorgasmia or delayed orgasm in women) and syndrome of inappropriate ADH (antidiuretic hormone) secretion (see section 4.4).

Metabolism and nutrition disorders: elevation or lowering of blood sugar levels, increased appetite and weight gain may be a drug reaction or due to relief of depression.

Hepato-biliary disorders: Rarely hepatitis (including altered liver function and jaundice).

Skin and subcutaneous tissue disorders: Increased perspiration and alopecia.

Renal and urinary disorders: Urinary frequency.

Investigations:

Common undesirable effect: Electrocardiogram QT prolonged

Confusion may occur at high doses or in elderly patients requiring reduction of dosage.

If your medicine is stopped too quickly you may suffer from feeling or being sick and headache. Even a gradual reduction in dose may cause dream and sleep disturbances, irritability and restlessness. These symptoms are not indicative of addiction .Mania or hypomania (exaggerated mood and/or elation) has been reported rarely within 2-7 days of stopping the tablets. Always follow your doctor's instructions on how you or your child should stop taking this medicine.

There have also been reports of withdrawal symptoms, respiratory depression and agitation in neonates, whose mothers received tricyclic antidepressants.

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.

Abrupt withdrawal after prolonged administration has caused nausea, headache and malaise. Gradual withdrawal of amitriptyline has been associated with transient symptoms such as irritability, restlessness,
and dream and sleep disturbances during the first two weeks of dosage reduction. These are not thought to be signs associated with addictions. Adverse reactions such as withdrawal symptoms, respiratory depression
and agitation have been reported in neonates whose mothers had taken tricyclic antidepressants in the last trimester of pregnancy.

Mania or hypomania have been reported rarely within 2-7 days of stopping therapy with tricyclic antidepressants.

Side-effects in enuresis: If this medicine is being taken to treat bed-wetting, the following side effects may occur although they are less frequent:, mild sweating, itching, changes in behaviour and The most common are drowsiness and anticholinergic effects. The recommended dosage must not be exceeded.

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.

4.9 Overdose

There is no specific antidote for tricyclic antidepressant poisoning. Patients should be hospitalised and treatment should be symptomatic and based on cardiac (including ECG monitoring) and respiratory support.

Symptoms

Toxicity is due to a combination of anticholinergic (antimuscarinic, atropine-like) effects at autonomic nerve endings and in the brain, cardiac sodium channel blockade and a1 adrenergic receptor blockade. In addition, tricyclic antidepressants block pre-synaptic uptake of amines and the cardiac delayed rectifier potassium channel (Ikr).

Features commonly include: sinus tachycardia, hot dry skin, dry mouth and tongue, dilated pupils, urinary retention and ileus, progressing to ataxia, nystagmus, divergent squint and drowsiness which may lead to deep coma and respiratory depression. Increased tone and hyperreflexia may be present with extensor plantar reflexes. In deep coma all reflexes (including brain-stem reflexes) may be abolished. Convulsions occur in >5% of cases and may herald haemodynamic compromise. ECG features include prolongation of the PR, QRS and QT intervals, non-specific ST segment and T wave changes and atrioventricular block.
Metabolic acidosis may be present. Hypotension may occur and may be severe.
Hypothermia and rhabdomyolysis may occur in patients who have been unconscious. Occasionally skin blisters may occur.

During recovery confusion, agitation and visual hallucinations may occur.
Features of serotonin toxicity may occur. These include CNS effects (including agitation or coma), autonomic instability (including hyperpyrexia), and neuromuscular excitability (including clonus and raised serum creatine kinase)
This syndrome is more likely to occur if the patient has been exposed to two or more drugs that increase the effect of serotonin in serotonergic synapses (by

increasing release, reducing reuptake or metabolism, or stimulating serotonin receptors), either as an acute overdose or if taken regularly, for example - SSRIs, MAOIs, tricyclic antidepressants, venlafaxine, tramadol, triptans, linezolid and St John's Wort; stimulant drugs of abuse (e.g. MDMA (ecstasy), amphetamines, cocaine, cathinone derivatives (mephedrone, etc)).

The cardiovascular and CNS effects in overdose will be potentiated by simultaneous ingestion of alcohol, cardiovascular agents and other psychotropic drugs

Management

Do not give flumazenil to reverse benzodiazepine toxicity in mixed overdoses.
1. Ensure a clear airway and adequate ventilation. Check arterial blood gases and correct any hypoxia. If hypercapnia is present assisted ventilation is indicated.
2. The benefit of gastric decontamination is uncertain. Consider activated charcoal by mouth or naso-gastric tube if the patient presents within 1 hour of ingestion of more than 5mg/kg, provided the airway can be protected.
A second dose of charcoal should be considered after 1 -2 hours in patients with features of toxicity who are able to swallow, or who have been intubated.
3. After cardiac arrest, prolonged resuscitation may be successful and should be continued for at least 1 hour.
4. Observe for at least 6 hours after ingestion. Monitor BP, pulse and cardiac rhythm. Repeat ECGs should be performed. Patients who remain asymptomatic and have a normal ECG by 6 hours are unlikely to develop late complications.
5. Check urea and electrolytes and monitor urine output. Check serum creatine kinase in patients who have been unconscious.
6. If metabolic acidosis persists despite correction of hypoxia and adequate fluid resuscitation consider correction with intravenous sodium bicarbonate. Rapid correction is particularly important if there is prolongation of the QRS or QT intervals.
7. Control convulsions with intravenous diazepam or lorazepam. Give oxygen and correct acid base and metabolic disturbances. Phenytoin is contraindicated in tricyclic overdosage (because in common with TCAs
it blocks sodium channels and may increase the risk of cardiac arrhythmias).
8. Correct hypotension by raising the foot of the bed. In severe cases administration of colloid to expand the intravascular volume is required (central venous pressure monitoring may be required). Alkalinisation with sodium bicarbonate may correct hypotension.
9. Agitated adults can be sedated with oral or IV diazepam. If ineffective consider oral or parenteral haloperidol.
10. Glucagon 10mg IV bolus may be given if patients are severely hypotensive.
11. If the patient is hypothermic, rewarm slowly using conventional means.
12. Monitor for rhabdomyolysis if the patient has been unconscious for a considerable time.
13. Forced diuresis, haemodialysis and haem perfusion are of no value due to the large volume of distribution of tricyclic antidepressants.
14. Other measures as indicated by the patient's clinical condition.

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

Amitriptyline is a tricyclic antidepressant with marked anticholinergic and sedative properties. Its mode of action in depression is not fully understood, though it is thought to increase the synaptic concentration of noradrenaline and serotonin in the CNS by inhibiting their re-uptake by the pre-synaptic neuronal membrane.

5.2 Pharmacokinetic properties

Amitriptyline is readily absorbed from the gastro-intestinal tract with peak plasma concentrations occurring within about 6 hours of oral administration. Since amitriptyline slows gastro-intestinal transit time, absorption may be delayed, particularly in over dosage. Onset of antidepressant activity takes 2-3 weeks.

Amitriptyline is extensively demethylated in the liver to its primary active metabolite, nortriptyline. The metabolism pathway includes N-oxidation and conjugation with glucuronic acid. Amitriptyline and nortriptyline are widely distributed throughout the body and are very highly bound to plasma and tissue protein. The estimated half-life of amitriptyline is 9-25 hours. It will cross the placental barrier and is excreted in breast milk. It is excreted in urine in the form of metabolites.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber other than those already provided in other sections of the SPC.

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

8 MARKETING AUTHORISATION NUMBER(S)

PL 17907/ 0131

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10 DATE OF REVISION OF THE TEXT

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