

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Amitriptyline Hydrochloride 25 mg/ 5 ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml of solution contains 25mg amitriptyline hydrochloride.

Excipients with known effect

Each 5ml of solution contains:

1mg propyl hydroxybenzoate (E216)

6mg methyl hydroxybenzoate (E218)

3.35g liquid maltitol

Approximately 10.5mg ethanol

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution.

A clear colourless to yellow solution with an orange/tangerine odour.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Amitriptyline is indicated for the treatment of:

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

-Nocturnal enuresis in children aged six years and above when organic pathology has been excluded and no response has been achieved to all other non-drug and drug treatments (used only as third line therapy). Amitriptyline should only be prescribed by a 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.

Adults - initial dosage: Usually 75mg a day in divided doses (or a single dose at night). If necessary, this may be increased to a total of 150mg a day, the additional doses being given in the late afternoon and/or at bedtime. The sedative effect is usually rapidly apparent. The antidepressant activity may be seen within three or four days or may take up to 30 days to develop adequately.

Adults - maintenance dosage: Usually 50 - 100mg a day. For maintenance therapy, the total dosage may be given in a single dose preferably in the evening or at bedtime. When satisfactory improvement has been reached, dosage should be reduced to the lowest amount that will maintain relief of symptoms. Maintenance therapy should be continued for three months or longer to lessen the chances of relapse.

Paediatric population

Children: Due to lack of clinical experience amitriptyline is not recommended for the treatment of depression in

children under 16 years of age.

Enuresis: Children aged 6 - 10 years may receive 10 - 20mg a day, while those aged 11 - 16 may need 25 - 50mg a day. 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 three 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.

Method of administration

For oral administration only.

4.3 Contraindications

- Co-administration with monoamine oxidase inhibitors
- prior sensitisation to amitriptyline
- during the recovery phase after myocardial infarction
- arrhythmias particularly heartblock of any degree
- mania
- severe liver disease
- porphyria
- lactation
- children under 6 years of age
- Hypersensitivity to tricyclic antidepressants or to any of the excipients listed in Section 6.1
- Congestive heart failure
- Coronary artery insufficiency
- Concomitant administration with drugs that prolong the QT interval. e.g. amiodarone, terfenadine, astemizole, sertindole, pimozide, thioridazine and sotalol.

See also sections 4.4 and 4.6.

4.4 Special warnings and precautions for use

Amitriptyline should be used with caution in patients with a history of epilepsy, and in patients with impaired liver function or phaeochromocytoma. Due to its atropine-like action, it should be used with caution in patients with a history of urinary retention, prostatic hypertrophy, narrow-angle glaucoma or increased intra-ocular pressure. In patients with narrow-angle glaucoma, even average doses may precipitate an attack of glaucoma. Nocturnal symptoms of gastro-oesophageal reflux may be aggravated if amitriptyline is given in the late evening to patients with hiatus hernia.

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.

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.

Blood sugar concentrations may be altered in diabetic patients.

Elderly patients can be particularly sensitive to the side-effects of tricyclic antidepressants (especially agitation, confusion and postural hypotension) and a reduced dose, especially initially, should be employed (see 4.2 Posology and method of administration).

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.

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 Undesirable Effects).

Sudden discontinuation of antidepressant therapy after regular administration for 8 weeks or more may precipitate withdrawal symptoms (see 4.8, Undesirable Effects).

Suicide/suicidal thoughts or clinical worsening

Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

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.

Amitriptyline should be used with caution in patients with blood dyscrasias.

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.

Excipient Warnings

This product contains liquid maltitol. Patients with rare hereditary problems of fructose should not take this medicine. Daily quantities of 10g or more may have a mild laxative effect. Calorific value 2.3 kcal/g maltitol.

Methyl and propyl hydroxybenzoates are contained in this product which may cause allergic reactions (possibly delayed).

This product contains small amounts of ethanol (alcohol), less than 100mg per dose

4.5 Interaction with other medicinal products and other forms of interaction

Alcohol: Amitriptyline may enhance the response to alcohol and increases the disulfiram (Antabuse) reaction of disulfiram with alcohol. Delirium has been reported in patients taking amitriptyline with disulfiram.

Anaesthetics: Increased risk of hypotension and cardiac arrhythmias during anaesthesia (see 4.4 Special warnings and precautions for use).

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

Analgesics: Increased anticholinergic side-effects with nefopam; increased analgesia with morphine. Increased risk of CNS toxicity when tricyclics given with tramadol.

Antiarrhythmics: Other drugs which prolong the QT interval, including amiodarone, disopyramide, procainamide, propafenone and quinidine, should be avoided because of the increased risk of prolonged QT interval and torsade de pointes.

Antibacterials: Plasma concentration reduced by rifampicin (reduced antidepressant effect). Concomitant use with linezolid may result in CNS excitation and hypertension. Increased risk of ventricular arrhythmias when tricyclics given with moxifloxacin –avoid concomitant use.

Anticholinergic agents: Excessive anticholinergic effects may occur when tricyclic antidepressants are combined with anticholinergic drugs. Paralytic ileus, urinary retention or acute glaucoma may be precipitated, especially in elderly patients. Amitriptyline for enuresis should not be combined with an anticholinergic drug.

Anticoagulants: Amitriptyline may increase or decrease anticoagulant activity - monitor prothrombin time.

Antidepressants: The concurrent use of antidepressants having varying modes of action should be made only with due recognition of their possible potentiation and with a thorough knowledge of their respective pharmacologies. Monoamine oxidase inhibitors 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. Fluoxetine markedly inhibits Cyt 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. Caution is also advised with reboxetine. After stopping tricyclics do not start moclobemide for at least 1 week.

St John's Wort: Tricyclic antidepressants should not be used with St John's wort. St John's Wort may decrease plasma levels of amitriptyline.

Antiepileptics: Tricyclic antidepressants may antagonise the anticonvulsant action of antiepileptics (convulsive threshold lowered). Carbamazepine may decrease the antidepressant action of amitriptyline. Sodium valproate can increase amitriptyline plasma levels.

Antifungals: Fluconazole may increase amitriptyline serum concentrations, potentiate QT interval prolongation and increase risk of torsade de pointes.

Antihistamines: Increased CNS depressant effects. Astemizole and terfenadine should be avoided due to increased risk of prolonged QT interval and torsade de pointes.

Antihypertensives: In general, the hypotensive effect of antihypertensives is enhanced by tricyclic antidepressants, but

amitriptyline may block the antihypertensive action of guanethidine, debrisoquine, betanidine and clonidine. Sudden withdrawal of amitriptyline from a patient stabilized on a postganglionic blocking agent may cause serious hypotension. All antihypertensive therapy should be reviewed following withdrawal of a tricyclic antidepressant as well as during treatment. (Refer also to Beta-blockers). There is an increased risk of hypertension on clonidine withdrawal.

Antipsychotics: Increased risk of prolonged QT interval and torsade de pointes with sertindole, pimozide and thioridazine – avoid concomitant use. Plasma concentrations of phenothiazines and amitriptyline may both be increased with concomitant use. Antipsychotics may lower convulsive threshold and increase risk of seizures with amitriptyline.

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. Increased risk of ventricular arrhythmias when tricyclics given with saquinavir – avoid concomitant use.

Anxiolytics and hypnotics: Enhanced sedation. 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.

Barbiturates and other CNS depressants: Enhanced response. Barbiturates may decrease the antidepressant action of amitriptyline.

Beta-blockers: Increased risk of prolonged QT interval and torsade de pointes with sotalol – avoid concomitant use.

CNS stimulants: Methylphenidate may increase the antidepressant action of amitriptyline.

Diuretics: Increased risk of postural hypotension.

Dopaminergics: Selegiline can potentiate effects of tricyclics and hyperpyretic crises, severe convulsions and fatalities have occurred. Tricyclics should not generally be given to patients receiving selegiline, or for at least two weeks after it has been discontinued. At least one week should elapse between withdrawing a tricyclic and starting selegiline. Concomitant use with entacapone should be avoided.

Muscle relaxants: Tricyclics enhance muscle relaxant effect of baclofen.

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

Oestrogens and progestogens: Oral contraceptives antagonise antidepressant effect (but side-effects may be increased due to increased plasma concentrations of amitriptyline).

Smoking: May reduce plasma concentration of amitriptyline.

Sympathomimetic agents: Amitriptyline should not be given with sympathomimetic agents such as adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine and phenylpropanolamine due to enhanced pressor response to these agents (hypertension, cardiac arrhythmias, etc), but local anaesthetics with adrenaline appear to be safe.

Thyroid hormone: Can accelerate the antidepressant response of tricyclic antidepressants but may precipitate cardiac arrhythmias.

Ulcer-healing agents: Cimetidine is reported to reduce hepatic metabolism of certain tricyclic antidepressants.

4.6 Fertility, pregnancy and lactation

The safety of amitriptyline for use during pregnancy has not been established.

Pregnancy

Amitriptyline is not recommended during pregnancy, especially during the first and third trimesters 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. Animal studies have shown harmful effects at 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. There have been reports of cardiac problems, irritability, respiratory distress, muscle spasms, seizures, and urinary retention in infants whose mothers received tricyclic antidepressants immediately prior to delivery.

Breast-feeding

Breast feeding mothers: Amitriptyline is detectable in breast milk. Due to the potential for serious adverse reactions in infants from amitriptyline, a decision should be made whether to discontinue breast feeding 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) should be avoided.

4.8 Undesirable effects

In general, amitriptyline is well tolerated. The side effects given below are essentially a combined list of all those of the tricyclic group of antidepressants. Some of them have not been reported with amitriptyline, but are included because of the similar pharmacologies of the group members. As the antidepressant effects of amitriptyline may not become apparent for the first 2-4 weeks of therapy, patients should be closely monitored during this period.

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

Immune system disorders: Skin rash, urticaria, photosensitisation, oedema of face and tongue.

Endocrine disorders: Syndrome of inappropriate ADH (antidiuretic hormone) secretion. Hyponatraemia (with drowsiness, confusion, or convulsions) may be associated with inappropriate secretion of antidiuretic hormone and may be more prevalent in the elderly.

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

Psychiatric disorders: Delirium (particularly in the elderly), delusions, hallucinations, mania, hypomania, excitement, anxiety, restlessness and agitation. Cases of suicidal ideation and suicidal behaviours have been reported during amitriptyline therapy or early after treatment discontinuation (see section 4.4). Increased or decreased libido, impotence, anorgasmia or delayed orgasm in women.

Nervous system disorders: Weakness, drowsiness, fatigue, headache, confusional states, disturbed concentration, disorientation, insomnia, nightmares, numbness, tingling and paraesthesia of the extremities, peripheral neuropathy, inco-ordination, ataxia, tremors, coma, convulsions, extrapyramidal symptoms including abnormal involuntary movements and tardive dyskinesia, dysarthria (more likely to occur with higher doses) and neuroleptic malignant syndrome. Anticholinergic effects include hyperpyrexia.

Eye disorders: Mydriasis. Anticholinergic effects include blurred vision, disturbance of accommodation, increased intra-ocular pressure.

Ear disorders: Tinnitus.

Cardiovascular disorders: Hypotension, syncope, postural hypotension, dizziness, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, sudden cardiac death, stroke, alteration of the ECG including dose-related non-specific ECG changes (generally without consequence) and changes in AV-conduction. Arrhythmias and severe hypotension are likely to occur with high dosage or overdose.

Gastro-intestinal disorders: Nausea, epigastric distress, vomiting, anorexia, stomatitis, unpleasant taste, diarrhoea, parotid swelling, black tongue. Anticholinergic effects include dry mouth, constipation, paralytic ileus.

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

Skin and subcutaneous tissue disorders: Increased perspiration, alopecia, pruritis.

Renal and urinary disorders: Urinary frequency. Anticholinergic effects include urinary retention, urinary tract dilatation.

Reproductive and breast disorders: Testicular swelling, gynaecomastia, breast enlargement, galactorrhoea, interference with sexual function (e.g. delayed ejaculation).

Investigations: Electrocardiogram QT prolonged (common).

Withdrawal symptoms

The symptoms associated with withdrawal, particularly after prolonged administration, include gastrointestinal disturbances such as nausea; generalised somatic symptoms such as headache, chills, increased perspiration and malaise; irritability, restlessness, anxiety and agitation; sleep disturbances (insomnia and vivid dreams); parkinsonism or akathisia; cardiac arrhythmias. These symptoms are not indicative of addictions. Withdrawal symptoms seem to be more common and more severe in children.

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 has been reported rarely within 2-7 days of stopping chronic therapy with tricyclic antidepressants.

Side effects in enuresis:

Behavioural changes have been observed in children receiving tricyclics for treatment of enuresis. Dosages used in enuresis are low compared with those used in depression and side effects are therefore less frequent. The most common are drowsiness and anticholinergic effects. The only other side effects, reported infrequently at these dosages, have been mild sweating and itching. The recommended dosage must not be exceeded.

Class effects

Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRs and TCAs. The mechanism leading to this risk is unknown.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting systems listed below:

HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2, Ireland;

Tel: +353 1 6764971;

Fax: +353 1 6762517.

Website: www.hpra.ie; e-mail: medsafety@hpra.ie

4.9 Overdose

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, cardiovascular agents and other psychotropic drugs.

Overdose effects are mainly due to anticholinergic (atropine-like) effects at autonomic nerve endings and in the brain.

There is also a quinidine-like effect on the myocardium.

Peripheral symptoms

Commonly include sinus tachycardia, hot dry skin, dry mouth and tongue, dilated pupils and urinary retention.

The most important ECG feature of toxicity is prolongation of the QRS interval, which indicates a high risk of ventricular tachycardia. In very severe poisoning the ECG may be bizarre. Rarely, prolongation of the PR interval or heart block may occur. QT interval prolongation and torsade de pointes has also been reported.

Central symptoms

Commonly include ataxia, nystagmus 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 may be abolished. A divergent squint may be present.

Hypotension and hypothermia may occur. Fits occur in >5% of cases.

Acidosis (metabolic and/or respiratory).

Ileus.

Rhabdomyolysis may occur in patients who have been unconscious. Occasionally skin blisters may occur.

In deep coma all reflexes (including brain-stem reflexes) may be abolished.

During recovery confusion, agitation and visual hallucinations may occur.

The Serotonin Syndrome may occur. Features of serotonin toxicity 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 serotenergic 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)).

Management

Do not give flumazenil to reverse benzodiazepine toxicity in mixed overdoses.

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.

An ECG should be taken and in particular the QRS interval should be assessed since prolongation signifies an increased risk of arrhythmia and convulsions. Give activated charcoal by mouth or naso-gastric tube if more than 4 mg/kg has been ingested within one hour, provided the airway can be protected. A second dose of charcoal should be considered after two hours in patients with central features of toxicity who are able to swallow.

Tachyarrhythmias are best treated by correction of hypoxia and acidosis. Even in the absence of acidosis 50 millimoles of sodium bicarbonate should be given by intravenous infusion to adults with arrhythmias or clinically significant QRS prolongation on the ECG.

Control convulsions with intravenous diazepam or lorazepam. Give oxygen and correct acid base and metabolic disturbances. Phenytoin is contraindicated in tricyclic overdosage, because, like tricyclic antidepressants, it blocks sodium channels and may increase the risk of cardiac arrhythmias. Glucagon has been used to correct myocardial depression and hypotension.

Ensure a clear airway and adequate ventilation, check arterial blood gases and correct any hypoxia. If hypercapnia is present assisted ventilation is indicated.

After cardiac arrest, prolonged resuscitation maybe successful and should be continued for at least 1 hour.

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.

Check urea and electrolytes and monitor urine output. Check serum creatine kinase in patients who have been unconscious.

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 QRS or QT intervals.

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).

Agitated adults can be sedated with oral or IV diazepam. If ineffective consider oral or parenteral haloperidol.

Forced diuresis, haemodialysis and haemoperfusion are of no value due to the large volume of distribution of tricyclic antidepressants.

If the patient is hypothermic, rewarm slowly using conventional means.

Monitor for rhabdomyolysis if the patient has been unconscious for a considerable time.

Since overdose is often deliberate, patients may attempt suicide by other means during the recovery phase. Deaths by deliberate or accidental overdose have occurred with this class of medication.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Tricyclic Antidepressants, ATC Code: N06A A09

Amitriptyline is a tricyclic antidepressant which mode of action in depression is not fully understood. It has anticholinergic and sedative properties.

It prevents the re-uptake of noradrenaline and serotonin at nerve terminals.

5.2 Pharmacokinetic properties

Amitriptyline is readily absorbed from the gastro intestinal tract. Peak plasma concentrations occur within about 6 hours of oral administration. Since amitriptyline slows gastro intestinal transit time, absorption may be delayed, particularly in overdosage. Amitriptyline is demethylated in the liver to the primary active metabolite, nortriptyline. The metabolism pathway includes N-oxidation and conjugation with glucuronic acid. It is distributed extensively into plasma and tissue protein. It has a half life from 9 to 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

None known

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methyl hydroxybenzoate (E218)
 Propyl hydroxybenzoate (E216)
 Propylene glycol
 Ascorbic acid
 Orange flavour 10950-56 (contains ethanol).
 Orange/tangerine flavour 10888-56 (contains ethanol).
 Sucralose powder
 Liquid maltitol
 Purified water

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened: 24 months
 After first opening: 1 month

6.4 Special precautions for storage

Do not store above 25°C.
 Store in the original bottle and outer carton in order to protect from light.

6.5 Nature and contents of container

150 ml amber soda glass (type III) bottle fitted with a 28 mm white child resistant tamper evident cap, with expanded polyethylene (EPE) liner, and outer cardboard carton.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Wockhardt UK Limited
 Ash Road North
 Wrexham
 LL13 9UF
 United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 1339/024/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 November 2010

10 DATE OF REVISION OF THE TEXT

September 2017