SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Amitriptyline 25 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains amitriptyline hydrochloride 25mg.

Excipients: contains lactose monohydrate 44.0 mg

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablets

Circular, biconvex, pale yellow film-coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

In the management of depression.

4.2 Posology and method of administration

Oral therapy: 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 75 mg a day in divided doses or as a single dose at night. If necessary, this may be increased to a total of 150 mg 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 – hospitalised patients: 100 mg a day may be required initially. This may be increased gradually to 200 mg a day if necessary. A small number of hospitalised patients may need as much as 300 mg a day.

Adults – maintenance dosage: Usually 50 mg to 100 mg 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.

Elderly patients: In general, lower dosages are recommended for these patients and an initial dose of 30 – 75 mg daily in divided doses is recommended, which should be increased slowly. A daily dosage of 50 mg may be satisfactory in elderly patients who may not tolerate higher dosages. The required dosage may be administered either as divided doses or as a single dose preferably in the evening or at bedtime.

Children: Due to lack of clinical experience, Amitriptyline Tablets are not recommended for the treatment of depression in children and adolescents under 18 years of age.

Plasma levels: Because of the wide variation in the absorption and distribution of tricyclic antidepressants in body fluids, dosage should be adjusted to clinical response and not based on plasma levels. However, plasma levels may be used as a guide to toxicity or non-compliance.

Route of administration

Oral.

4.3 Contraindications

1. Use in patients who are currently receiving, or have received within two weeks, monoamine oxidase inhibitors.

2. Use in patients in the acute phase of myocardial infarction.

3. Hypersensitivity to amitriptyline (or any other dibenzazepine) or to any of the excipients listed in 6.1.

4. Use in the management of depression in children and adolescents under the age of 18 years.

5. Use in patients with cardiac arrhythmias, particularly heartblock or severe liver dysfunction.

6. Use during lactation in women breast-feeding infants.

4.4 Special warnings and precautions for use

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

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present. The risk of suicide remains during treatment of depressed patients and until significant remission occurs. Such patients require careful supervision.

General:
Amitriptyline should not be used in the treatment of children and adolescents under the age of 18 years. Studies in depression in this age group did not show a beneficial effect for tricyclic antidepressants. Studies with other classes of antidepressants (e.g. Selective serotonin re-uptake inhibitors, MAO inhibitors) have shown a risk of suicidality, self-harm and hostility related to these compounds. The risk cannot be excluded with amitriptyline. In addition, amitriptyline is associated with a risk of cardiovascular adverse events in all age groups. Furthermore, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are not available (see also section 4.8 Undesirable effects and section 4.9 Overdose).

Amitriptyline should be used with caution in patients with a history of epilepsy or recent convulsions, in patients with impaired liver function and, because of its atropine-like action, in patients with a

history of urinary retention, closed-angle glaucoma, or increased intra-ocular pressure. In patients with closed-angle glaucoma, even average doses may precipitate an attack of glaucoma.

Tricylic antidepressants including amitriptyline may cause QT interval prolongation, torsade de pointes, and sudden cardiac death. Risk factors include family history, age, female gender, metabolic and cardiovascular disease, metabolic inhibitors, hypokalemia, drug overdose, and co-prescription of drugs associated with QT interval prolongation. Clinicians should be cautious when prescribing tricyclic antidepressants with other drugs such as thioridazine that are capable of prolonging the QT interval.

There has been a report of fatal dysrhythmia as late as 56 hours after amitriptyline overdose.

Amitriptyline should be discontinued several days before elective surgery, if possible. If patients require urgent surgery, the anaesthetist should be informed of medications in advance, in view of the risk of cardiovascular complications.

Hyperpyrexia has been reported when tricyclic antidepressants are administered with anticholinergic agents or with neuroleptic drugs, particularly during hot weather.

Elderly patients are particularly liable to experience adverse reactions: especially agitation, confusion, and postural hypotension.

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

Cardiovascular/endocrine disorders:
Patients with cardiovascular disorders, hyperthyroid patients and those receiving thyroid medication should be closely supervised and the dosage of all medications carefully adjusted.

Central nervous system disorders:
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.

Unless essential it is inadvisable to combine amitriptyline and electroconvulsive therapy (ECT) (see section 4.5 “Interactions”).

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

4.5 Interaction with other medicinal products and other forms of interaction

Other antidepressant drugs: The concurrent use with antidepressants having varying modes of action should only be made with due recognition of their possible potentiation and with a thorough knowledge of their respective pharmacologies. Monoamine oxidase inhibitors (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 an MAOI and starting amitriptyline, which should be introduced cautiously and dosage increased gradually.

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

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

Guanethidine: Amitriptyline may block the antihypertensive action of guanethidine or similarly acting compounds.

Anticholinergic agents/sympathomimetic drugs: Amitriptyline should not be given with anticholinergic or sympathomimetic agents including adrenaline combined with local anaesthetics. Paralytic ileus may occur in patients taking tricyclic antidepressants combined with drugs having an anticholinergic action.

Cimetidine: Cimetidine is reported to reduce hepatic metabolism of certain tricyclic antidepressants.

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

Antipsychotics: Increased risk of prolonged QT interval and torsade de pointes with sertindole, pimozide and thioridazine – avoid concomitant use.

Central nervous system depressants: Amitriptyline may enhance the response to alcohol, barbiturates, and other CNS depressants. Caution is advised if patients receive large doses of ethchlorvynol concurrently. Transient delerium has been reported in patients treated with 1g ethchlorvynol and 75 mg to 150 mg of amitriptyline.

Disulfiram: Delirium has been reported in patients taking both amitriptyline and disulfiram.

Thyroid preparations: Concomitant administration of thyroid preparations can potentiate the effects of amitriptyline. Isolated cases of paroxysmal atrial tachycardia, thyrotoxicosis and hypothyroidism due to concurrent therapy have been described.

Fluconazole: Fluconazole is reported to reduce the metabolism of amitriptyline.

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

4.6 Fertility, pregnancy and lactation

The safety of amitriptyline for use during pregnancy and lactation has not been established. The possible benefits of using amitriptyline should be weighed against possible hazards to the foetus, child or mother. Use of high doses in animals has resulted in embryotoxicity and clinical experience has been limited.

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

4.7 Effects on ability to drive and use machines

This drug may cause drowsiness or affect concentration. Patients receiving this medication should not drive or operate machinery unless it has been shown not to interfere with physical or mental capacity.

4.8 Undesirable effects

In general amitriptyline is well tolerated. The side effects given below are essentially a combined list of all of 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 two to four weeks of therapy, patients should be closely monitored during this period.

Cardiovascular reactions: hypotension, syncope, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke, non-specific ECG changes and changes in AV conduction. QT interval prolongation and torsade de pointes.

CNS and neuromuscular: confusional states, disturbed concentration, disorientation, delusions, hallucinations, excitement, anxiety, restlessness, drowsiness, insomnia, nightmares, numbness, tingling, and paraesthesiae of the extremities, peripheral neuropathy, incoordination, ataxia, tremors,

coma, convulsions, alteration of the EEG, extrapyramidal symptoms including abnormal involuntary movements and tardive dyskinesia, dysarthria, tinnitus.

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

Anticholinergic: dry mouth, blurred vision, mydriasis, disturbance of accommodation, increased intra-ocular pressure, constipation, paralytic ileus, hyperpyrexia, urinary retention, urinary tract dilation.

Allergic: skin rash, urticaria, photosensitization, oedema of face and tongue.

Haematological: bone-marrow depression including agranulocytosis, leucopenia, eosinophilia, purpura, thrombocytopenia.

Gastro-intestinal: nausea, epigastric distress, vomiting, anorexia, stomatitis, unpleasant taste, diarrhoea, parotid swelling, black tongue, rarely hepatitis (including altered liver function and jaundice).

Endocrine: testicular swelling, gynaecomastia, breast enlargement, galactorrhoea, increased or decreased libido, impotence, elevation or lowering of blood sugar levels, syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Other reactions: dizziness, weakness, fatigue, headache, oedema, weight gain or loss, increased perspiration, urinary frequency, alopecia. Abrupt withdrawal after prolonged administration has caused nausea, headache and malaise. Reports have associated gradual withdrawal with transient symptoms including irritability, restlessness, as well as dream and sleep disturbances during the first two weeks of dosage reduction. These symptoms are not indicative of addiction.

Rare instances of mania and hypomania have been reported within 2 – 7 days of stopping chronic therapy and tricyclic antidepressants.

Class effects: Epidemiological studies, mainly 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 the risk is unknown.

Side effects – causal relationship unknown: The following additional side effects have been reported. However, a causal relationship to therapy with amitriptyline has not been established; lupus-like syndrome (migratory arthritis, positive ANA and rheumatoid factor).

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 preferably through the online reporting option accessible from the IMB homepage. A downloadable report form is also accessible from the IMB website, which may be completely manually and submitted to the IMB via “freepost”. Alternatively, the traditional post-paid ‘yellow card’ option may also continue to be used.

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4.9 Overdose

High dosage may cause temporary confusion, disturbed concentration, or transient visual hallucinations. Overdosage may cause drowsiness; hypothermia; tachycardia and other arrhythmic abnormalities, such as bundle branch block; ECG evidence of impaired conduction; congestive heart failure; dilated pupils; disorders of ocular motility; convulsions; severe hypotension; stupor, coma, and polyradiculoneuropathy; constipation. Other symptoms may be agitation, hyperactive reflexes, muscle rigidity, vomiting, hyperpyrexia or any of those listed under "Undesirable effects."

All persons suspected of having taken an overdosage should be admitted to hospital as soon as possible. Treatment is symptomatic and supportive. The stomach should be emptied as quickly as possible by emesis, followed by gastric lavage upon arrival at hospital. Following lavage, activated charcoal may be given; 20 to 30g every four to six hours during the first 24 to 48 hours after ingestion. An ECG should be taken and close monitoring of cardiac function initiated if there is any sign of abnormality. An open airway and an adequate fluid intake should be maintained and body temperature regulated.

Intravenous physostigmine salicylate, 1 mg to 3 mg, has been reported to reverse the symptoms of tricyclic antidepressant poisoning.

Because physostigmine is rapidly metabolised, the dosage of physostigmine should be repeated as required, particularly if life-threatening signs such as arrhythmias, convulsions, and deep coma recur or persist after the initial dose of physostigmine. Because physostigmine itself may be toxic, it is not recommended for routine use.

Standard measures should be used to manage circulatory shock and metabolic acidosis. Cardiac arrhythmias may be treated with neostigmine, pyridostigmine or propranolol. Should cardiac failure occur, use of digitalis should be considered. Close monitoring of cardiac function for not less than five days is advisable.

If convulsions occur, they should be treated with paraldehyde, diazepam, or an inhalation anaesthetic. Barbiturates should not be used because amitriptyline increases their CNS-depressant action.

Dialysis is of no value because of low plasma concentrations of amitriptyline. 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

Amitriptyline is a tricyclic anti-depressant. It has marked antimuscarinic and sedative properties, and prevents the re-uptake (and hence inactivation) of noradrenaline and serotonin at nerve terminals. Its mode of action in depression is not fully understood. The principal effects of the tricyclic antidepressants on the function of the autonomic nervous system are those that result from inhibition of norepinephrine transport into adrenergic nerve terminals and from antagonism of muscarinic, cholinergic, and 1-adrenergic responses to the autonomic neurotransmitters.

5.2 Pharmacokinetic properties

Amitriptyline is readily absorbed from the gastro-intestinal tract, peak plasma concentrations occurring within about 6 hours of oral administration. Since amitriptyline slows gastro-intestinal transit time, absorption can, however, be delayed, particularly in overdosage. Amitriptyline is extensively demethylated in the liver to its primary active metabolite, nortriptyline.

Paths of metabolism of both amitriptyline and nortriptyline include hydroxylation (possibly to active metabolites) and N-oxidation. Amitriptyline is excreted in the urine, mainly in the form of its metabolites, either free or in conjugated form.

Amitriptyline and nortriptyline are widely distributed throughout the body and are extensively bound to plasma and tissue protein. Amitriptyline has been estimated to have a half-life ranging from 9 to 25 hours, which may be considerably extended in overdosage.

Plasma concentrations of amitriptyline and nortriptyline vary very widely between individuals and no simple correlation with therapeutic response has been established.

5.3 Preclinical safety data

No further information provided.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Maize starch
Povidone
Microcrystalline cellulose
Purified talc
Colloidal anhydrous silica
Magnesium stearate

Film-coating:
Propylene glycol
Hypromellose
Talc
Yellow iron oxide (E172)
Titanium dioxide (E171)
Quinoline yellow aluminium lake (E104)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years

6.4 Special precautions for storage

Do not store above 25ºC

6.5 Nature and contents of container

Polypropylene tubes with low density polyethylene caps. High density polyethylene film may be used as packing material.
Pack sizes: 50, 100, 250, 500 and 1,000 tablets.

PVC/AL transparent blisters
Pack sizes: 50, 100 and 250 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Limited
Waterford Road
Clonmel
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8 MARKETING AUTHORISATION NUMBER

PA 126/41/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:	15th March 1985
Date of last renewal:	15th March 2010

10 DATE OF REVISION OF THE TEXT

September 2013