

1 NAME OF THE MEDICINE

Amitriptyline hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ENDEP tablets contain 10 mg, 25 mg or 50 mg of amitriptyline hydrochloride as the active ingredient.

Excipients with known effect in 10 mg tablet: Sugars as lactose, soya bean products and traces of sulfites.

Excipients with known effect in 25 mg and 50 mg tablet: Sugars as lactose and traces of sulfites.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

ENDEP 10: 7 mm normal convex, blue film coated tablet debossed with 'AP 10' on one side and α on the other.

ENDEP 25: 7 mm yellow film coated normal convex tablet marked 'AP/25' on one side, α on reverse.

ENDEP 50: 8 mm hexagonal tan film coated tablet marked 'AP 50' on one side, α on reverse.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For the treatment of major depression. ENDEP 50 mg tablets are indicated only for the maintenance treatment of major depression (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Nocturnal enuresis where organic pathology has been excluded.

4.2 DOSE AND METHOD OF ADMINISTRATION

Depression

Dosage considerations. Dosage should be initiated at a low level and increased gradually, noting carefully the clinical response and any evidence of intolerance.

Initial dosage for outpatient adults. 75 mg a day in divided doses is usually satisfactory. If necessary, this may be increased to a total of 150 mg a day. Increases are made preferably in the late afternoon and/or bedtime doses. The sedative effect is usually rapidly apparent. The antidepressant activity may be evident within three or four days or may take up to 30 days to develop adequately.

Alternative methods for initiating therapy in outpatients are: begin therapy with 50 to 100 mg preferably in the evening or at bedtime; this may be increased by 25 to 50 mg as necessary to a total of 150 mg per day.

Dosage for hospitalised patients. 100 mg a day may be required initially. This can be increased gradually to 200 mg a day if necessary. A small number of hospitalised patients may need as much as 300 mg per day.

Dosage for elderly patients. In general, lower dosages are recommended for these patients. 50 mg daily may be satisfactory in those elderly patients who may not tolerate higher doses. The required daily dose may be administered either in divided doses or as a single dose preferably in the evening or at bedtime.

Maintenance dosage. Usually from 50 to 100 mg per day. For maintenance therapy, the total daily 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. It is appropriate to continue maintenance therapy 3 months or longer to lessen the possibility of relapse.

Enuresis

A dose of 10 mg at bedtime has been found effective in children under 6 years of age. In older children, the dosage should be increased as necessary according to weight and age. Children 6 to 10 years of age may receive 10 to 20 mg per day. In the age group from 11 to 16, a dose of 25 to 50 mg at bedtime may be required.

Most patients respond in the first few days of therapy. In those who do respond, the tendency is for increasing, continued improvement as the period of treatment is extended. Continued treatment is usually required to maintain the response until control is established.

The doses of ENDEP recommended in the treatment of enuresis are low compared with those used in the treatment of depression, even allowing for differences in age and weight. This recommended dose must not be exceeded. This medication should be kept out of reach of children.

Plasma Levels

Because of the wide variation in the absorption and distribution of tricyclic antidepressants in body fluids, it is difficult to directly correlate plasma levels and therapeutic effect. However, determination of plasma levels may be useful in identifying patients who appear to have toxic effects and may have excessively high levels, or those in whom lack of absorption or non-compliance is suspected. Adjustments in dosage should be made according to the patient's clinical response and not on the basis of plasma levels.

4.3 CONTRAINDICATIONS

Amitriptyline is contraindicated in patients who have shown prior hypersensitivity to it.

Monoamine Oxidase Inhibitors (MAOIs)

ENDEP should not be given concurrently with monoamine oxidase inhibitors, including selegiline. The combination of amitriptyline with a monoamine oxidase inhibitor has caused severe convulsions, hyperpyretic crises and death. When it is desired to substitute amitriptyline for a monoamine oxidase inhibitor, a minimum of 14 days should be allowed to elapse after the latter is discontinued. Amitriptyline should then be initiated cautiously with gradual increase in dosage until optimum response is achieved.

Cisapride

Amitriptyline is contraindicated in patients taking cisapride due to the possibility of adverse cardiac interactions including prolongation of the QT interval, cardiac arrhythmias and conduction system disturbances.

Myocardial Infarction

Amitriptyline is not recommended for use during the acute recovery phase following myocardial infarction.

See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.6 FERTILITY, PREGNANCY AND LACTATION.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Clinical Worsening and Suicide Risk associated with Psychiatric Disorders

The risk of suicide attempt is inherent in depression and may persist until significant remission occurs. This risk must be considered in all depressed patients.

Patients with depression, both adult and paediatric, may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviour (suicidality), whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored for clinical worsening and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms.

Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition and/or the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present. Patients with co-morbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behaviour (suicidality) in children, adolescents and young adults (ages 18-24) with major depressive disorder and other psychiatric disorders. Short term-studies did not show an increase in risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

Pooled analyses of 24 short-term (4 to 16 weeks), placebo-controlled trials of nine antidepressant medicines (SSRIs and others) in 4400 children and adolescents with major depressive disorder (16 trials), obsessive compulsive disorder (4 trials), or other psychiatric disorders (4 trials) have revealed a greater risk of adverse events representing suicidal behaviour or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients treated with an antidepressant was 4%, compared with 2% of patients given placebo. There was considerable variation in risk among the antidepressants, but there was a tendency towards an increase for almost all antidepressants studied. The risk of suicidality was most consistently observed in the major depressive disorder trials, but there were signals of risk arising from trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in these trials. It is unknown whether the suicidality risk in children and adolescent patients extends to use beyond several months. The nine antidepressant medicines in the pooled analyses included five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and four non-SSRIs (bupropion, mirtazapine, nefazodone, venlafaxine).

The pooled analyses of placebo-controlled trials in adults with major depressive disorder or other psychiatric disorders included a total of 295 short-term trials (average duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. Absolute risk of suicidality varied across the different indications, with the highest incidence in major depressive disorder. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

Table 1	
Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	<i>Drug-Related Increases</i>
<18	14 additional cases
18-24	5 additional cases
	<i>Drug-Related Decreases</i>
25-64	1 fewer case
≥65	6 fewer cases

There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e. beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adults, adolescents and children being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric. Although a causal link between the emergence of such symptoms and either worsening of depression and/or emergence of suicidal impulses has not been established, there is concern that such symptoms may be precursors of emerging suicidality.

Families and caregivers of children, adolescents and young adults (ages 18-24) being treated with antidepressants for major depressive disorder or for any other condition (psychiatric or non-psychiatric) should be informed about the need to monitor these patients for the emergence of agitation, irritability, unusual changes in behaviour, and other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. It is particularly important that monitoring be undertaken during the initial few months of antidepressant treatment or at times of dose increase or decrease.

Prescriptions for ENDEP should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

ENDEP 50 mg Tablets

The 50 mg tablets are indicated only for the maintenance treatment of major depression. The 50 mg tablets should not be used in acutely ill patients where there is a risk of suicide. There is an increased risk of completed suicide by overdose with the 50 mg tablet compared with the 25 mg tablet.

To prevent accidental overdose and the potentially fatal consequences, patients should be made aware of the unusual toxicity of tricyclic antidepressants and the need to maintain strict control over the tablets as well as the need to store them out of reach of children.

Bipolar Disorder and Activation of Mania/Hypomania

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed that treating such an episode with an antidepressant alone can increase the likelihood of precipitation of a mixed/manic episode in patients at risk of bipolar disorder. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include detailed psychiatric history, including a family history of suicide, bipolar disorder and depression.

Seizures

ENDEP should be used with caution in patients with a history of seizures.

Central Nervous Disorders

The possibility of suicide in depressed patients remains during treatment. Patients should not have access to large quantities of this medicine during treatment.

When amitriptyline hydrochloride is used to treat the depressive component of schizophrenia, psychotic symptoms may be aggravated. Likewise, in manic depressive psychosis, depressed patients may experience a shift toward the manic phase. Paranoid delusions, with or without associated hostility, may be exaggerated. In

any of these circumstances, it may be advisable to reduce the dose of amitriptyline or to use a major tranquillising medicine, such as perphenazine, concurrently.

Glaucoma

Due to its atropine-like action, ENDEP should be used with caution in patients with narrow angle glaucoma or increased intraocular pressure. In patients with narrow angle glaucoma, even average doses precipitate an attack.

Severe Cutaneous Reactions

Severe cutaneous adverse reactions (SCARs) including drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported in association with amitriptyline treatment. Most of these reactions occurred within 2 to 6 weeks. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for cutaneous reactions. If signs and symptoms suggestive of these reactions appear, ENDEP should be withdrawn immediately, treatment with ENDEP must not be restarted in this patient at any time and, an alternative treatment should be considered (as appropriate).

Cardiovascular Disorders

Patients with cardiovascular disorders should be watched closely. Tricyclic antidepressant medicines, including amitriptyline hydrochloride, particularly when given in high doses, have been reported to produce arrhythmias, sinus tachycardia, and prolongation of the conduction time. Myocardial infarction and stroke have been reported with medicines of this class.

Endocrine Disorders

Close supervision is required when amitriptyline is given to hyperthyroid patients or those receiving thyroid medication (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Other Antidepressant Medicines

The addition of other antidepressant medicines generally does not result in any additional therapeutic benefit. Untoward reactions have been reported after the combined use of antidepressant agents having varying modes of activity. Therefore, combined use of amitriptyline hydrochloride and other antidepressant medicines should be undertaken only with due recognition of the possibility of potentiation and with a thorough knowledge of the pharmacology of both medicines. There has been no evidence of potentiation when patients receiving amitriptyline hydrochloride were changed immediately to protriptyline or vice versa.

See Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

Elective Surgery

Discontinue the medicine several days before elective surgery if possible.

Impairment of Motor Co-ordination

ENDEP may impair alertness in some patients; See Section 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES.

Use in Hepatic Impairment

In the presence of hepatic disease, amitriptyline should be used cautiously.

Use in Renal Impairment

Due to its atropine-like action, ENDEP should be used with caution in patients with a history of urinary retention.

Use in the Elderly

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Paediatric Use

The safety and efficacy of ENDEP for the treatment of depression or other psychiatric disorders in children and adolescents aged less than 18 years has not been satisfactorily established. ENDEP should not be used in this age group for the treatment of depression.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Other antidepressant medicines. A potentially lethal interaction can occur between monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants. It is advisable to discontinue the MAOI for at least 2 weeks before taking ENDEP (see Section 4.3 CONTRAINDICATIONS).

Concurrent use of fluoxetine and tricyclic antidepressants has produced increased plasma concentrations of the tricyclic antidepressants. Some clinicians recommend dosage reductions for tricyclic antidepressants of about 50% if used concurrently with fluoxetine. Any patient receiving amitriptyline and fluoxetine concurrently should be observed closely for adverse effects and consideration should be given to monitoring the plasma levels of the tricyclic antidepressant with dosage reduction where necessary.

There have been no reports of untoward events when patients receiving amitriptyline hydrochloride were changed immediately to protriptyline or vice versa.

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

Anticholinergic agents/sympathomimetic medicines. When amitriptyline is given with anticholinergic agents or sympathomimetic medicines, including adrenaline (epinephrine) combined with local anaesthetics, close supervision and careful adjustment of dosage are required. Paralytic ileus may occur in patients taking tricyclic antidepressants in combination with anticholinergic type medicines.

Anticholinergic agents/neuroleptic medicines. Hyperpyrexia has been reported when tricyclic antidepressants are administered with anticholinergic agents or with neuroleptic medicines, particularly during hot weather. Concurrent use of phenothiazines and tricyclic antidepressants have the potential to elevate plasma levels of both agents. The sedative and anticholinergic effects may be prolonged and the risk of seizures and neuroleptic malignant syndrome increased.

Medicines Metabolised By Cytochrome P450 2D6. Concomitant use of tricyclic antidepressants with medicines that can inhibit cytochrome P450 2D6 (e.g. quinidine; cimetidine) and those that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the Type 1C antiarrhythmics, e.g. flecainide) may require lower doses than usually prescribed for either the tricyclic antidepressant or the other medicine. Whenever one of these other medicines is withdrawn from co-therapy, an increased dose of tricyclic antidepressant may be required. While all the selective serotonin reuptake inhibitors (SSRIs), e.g. fluoxetine, sertraline and paroxetine, inhibit P 450 2D6, they may vary in the extent of inhibition.

Cimetidine is reported to reduce hepatic metabolism of certain tricyclic antidepressants, thereby delaying elimination and increasing steady state concentrations of these medicines.

Central nervous system depressants. Amitriptyline may enhance the response to alcohol and the effects of barbiturates and other CNS depressants.

Disulfiram. Delirium has been reported with concurrent administration of amitriptyline and disulfiram.

Electroshock therapy. Concurrent administration of amitriptyline and electroshock therapy may increase the hazards of therapy. Such treatment should be limited to patients for whom it is essential.

Antithyroid medicines. Concurrent use may increase the risk of agranulocytosis.

Thyroid hormones. Concurrent use with tricyclic antidepressants may increase the therapeutic and toxic effects of both medications. Toxic effects include cardiac arrhythmias and CNS stimulation.

Analgesics. Tricyclic antidepressants may enhance the seizure risk in patients taking tramadol.

Selective Serotonin Reuptake Inhibitors (SSRIs). The "serotonin syndrome" (alterations in cognition, behaviour, autonomic nervous system function, and neuromuscular activity) has been reported with amitriptyline when given concomitantly with other serotonin-enhancing medicines including Selective Serotonin Reuptake Inhibitors (SSRIs).

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

Other medicines. Because tricyclic antidepressants may delay gastric emptying and decrease intestinal motility, careful dosage monitoring is essential with any medicine that may be subject to gastric inactivation (ie. levodopa) or which may be absorbed to a greater extent because of the increased time available for absorption (ie. anticoagulants).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No data available.

Use in Pregnancy

Pregnancy Category: C

Withdrawal symptoms in newborn infants have been reported with prolonged maternal use of this class of medicines.

Tricyclic antidepressants have not been shown to be associated with an increased incidence of birth defects. However, there is evidence of interference with central monoamine neurotransmission in rats. Care should be taken that there are sound indications for the use of these antidepressants in pregnancy.

There are no well controlled studies in pregnant women; therefore, in administering amitriptyline to pregnant women, the potential benefits must be weighed against the possible hazards to mother and child.

Use in Lactation

Amitriptyline is detectable in breast milk. Because of the potential for serious adverse effects in infants from amitriptyline, a decision should be made whether to discontinue nursing or discontinue the medicine.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

ENDEP may cause drowsiness, impair alertness in some patients and increase the effects of alcohol. Patients should be instructed not to drive a motor vehicle, operate machinery and/or undertake activities that may be hazardous in the context of diminished alertness if they are affected by ENDEP.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Note. Included are a few adverse effects which have not been reported with this specific medicine. However, pharmacological similarities among the tricyclic antidepressants require that each of the effects be considered when amitriptyline is administered.

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).

Metabolism and nutrition disorders

Rare: decreased appetite.

Frequency not known: elevation or lowering of blood sugar levels, increased appetite, anorexia.

Cardiac disorders

Very common: tachycardia, palpitations.

Common: atrioventricular block, bundle branch block.

Uncommon: collapse conditions, worsening of cardiac failure.

Rare: arrhythmias.

Very rare: cardiomyopathies, torsades de pointes.

Frequency not known: hypersensitivity myocarditis, myocardial infarction.

Vascular disorders

Very common: orthostatic hypotension.

Uncommon: hypertension.

Frequency not known: hyperthermia, stroke, syncope.

Nervous system and neuromuscular disorders

Very common: somnolence, tremors, dizziness, headache, drowsiness, speech disorders (dysarthria).

Common: disturbance in attention, dysgeusia, paraesthesia (of the extremities), ataxia.

Uncommon: convulsions.

Very rare: akathisia, polyneuropathy.

Frequency not known: weakness, disturbed concentration disorder, disorientation, delusions, excitement, restlessness, numbness, tingling, peripheral neuropathy, incoordination, coma, seizures, alteration in EEG patterns, extrapyramidal disorder including abnormal voluntary movements and tardive dyskinesia.

Psychiatric disorders

Very common: aggression.

Common: confusional states, libido decrease, agitation.

Uncommon: hypomania, mania, anxiety, insomnia, nightmares.

Rare: delirium (in elderly patients), hallucinations, suicidal thoughts or behaviour*

Frequency not known: paranoia.

*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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Skin and subcutaneous tissue disorders

Very common: hyperhidrosis.

Uncommon: rash, urticaria, pruritus, oedema of face and tongue.

Rare: alopecia, photosensitisation.

Not known: severe cutaneous adverse reactions (SCARs), including drug reaction with eosinophilia and systemic symptoms (DRESS).

Blood and lymphatic system disorders

Rare: bone marrow depression including agranulocytosis, leucopenia, eosinophilia, purpura and thrombocytopenia.

Respiratory, thoracic and mediastinal disorders

Very common: congested nose.

Very rare: allergic inflammation of the pulmonary alveoli and of the lung tissue, respectively (alveolitis, Löffler's syndrome).

Gastrointestinal disorders

Very common: dry mouth, constipation, nausea.

Uncommon: diarrhoea, vomiting.

Rare: parotid swelling (salivary gland enlargement), paralytic ileus.

Frequency not known: epigastric distress, stomatitis, peculiar taste, black tongue.

Hepatobiliary disorders

Rare: jaundice, hepatitis.

Uncommon: hepatic impairment (e.g. cholestatic liver disease).

Eye disorders

Very common: disturbance of accommodation.

Common: mydriasis.

Very rare: acute glaucoma.

Frequency not known: blurred vision, dry eye.

Ear and labyrinth disorders

Uncommon: tinnitus.

Renal and urinary disorders

Common: micturition disorders, erectile dysfunction.

Uncommon: urinary retention.

Frequency not known: urinary frequency, dilatation of urinary tract, syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Reproductive system and breast disorders

Common: erectile dysfunction.

Uncommon: galactorrhoea.

Rare: gynaecomastia.

Frequency not known: testicular swelling, breast enlargement, increased or decreased libido, interference with sexual function including impotence.

General disorders and administration site conditions

Common: fatigue, feelings of thirst, oedema, increased perspiration, drowsiness, hyperpyrexia.

Rare: pyrexia.

Investigations

Very common: weight gain.

Common: nonspecific ECG changes and changes in AV conduction, electrocardiogram QT prolonged, electrocardiogram QRS complex prolonged, hyponatremia.

Uncommon: increased intraocular pressure.

Rare: weight loss, liver function test abnormal, blood alkaline phosphatase increased, transaminases increased.

Serotonin Syndrome. The “serotonin syndrome” (alterations in cognition, behaviour, autonomic nervous system function, and neuromuscular activity) has been reported with amitriptyline when given concomitantly with other serotonin-enhancing medicines.

Withdrawal symptoms. Abrupt cessation of treatment after prolonged administration may produce nausea, headache and malaise. Gradual dosage reduction has been reported to produce, within two weeks, transient symptoms including irritability, restlessness, and dream and sleep disturbance. These are not indicative of addiction. Rare instances have been reported of mania or hypomania occurring within 2 to 7 days following cessation of chronic therapy with tricyclic antidepressants.

In enuresis. The doses of ENDEP recommended in the treatment of enuresis are low compared with those used in the treatment of depression, even allowing for differences in age and weight. Consequently, side effects are less frequent than when the medicine is used in treating depression. The most common side effects are drowsiness and anticholinergic effects.

Causal relationship unknown. A lupus-like syndrome (migratory arthritis, positive ANA and rheumatoid factor) has been reported rarely; however, a causal relationship to therapy with amitriptyline could not be established.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Deaths by deliberate or accidental overdosage have occurred with this class of medicine.

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

Symptoms

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

Cardiac symptoms: arrhythmic (ventricular tachyarrhythmias, torsade de pointes, ventricular fibrillation) and other abnormalities such as bundle branch block, ECG evidence of impaired conduction, congestive heart failure. The ECG characteristically shows a 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. Changes in the electrocardiogram, particularly in QRS axis or width, are clinically significant indicators of tricyclic antidepressant toxicity. Widening of the QRS-complex usually correlates well with the severity of the toxicity following acute overdoses. Hypotension, cardiogenic shock. Metabolic acidosis, hypokalemia, hyponatraemia.

High doses may cause temporary confusion, disturbed concentration, or transient visual hallucinations. Overdosage may cause drowsiness, hypothermia, dilated pupils, stupor, and polyradiculoneuropathy. Other symptoms may be agitation, muscle rigidity, vomiting, hyperpyrexia, or any of those listed under Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

Overdose with amitriptyline in children could have serious consequences. Children are especially susceptible to coma, cardiotoxicity, respiratory depression, seizures, hyponatraemia, lethargy, sinus tachycardia, drowsiness, nausea, vomiting and hyperglycaemia.

Treatment

All patients suspected of having taken an overdosage should be admitted to a hospital as soon as possible. Treatment is symptomatic and supportive. Activated charcoal may reduce absorption of the medicine if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected. An ECG should be taken and close monitoring of cardiac function instituted if there is any sign of abnormality. Maintain an open airway and adequate fluid intake; regulate body temperature.

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

Anticonvulsants may be given to control convulsions. Amitriptyline increases the CNS depressant action but not the anticonvulsant action of barbiturates; therefore, an inhalation anaesthetic or diazepam is recommended for control of convulsions.

Dialysis is of no value because of low plasma concentrations of the medicine.

Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Amitriptyline is a tricyclic antidepressant with sedative properties.

Mechanism of Action

The mechanism of action of amitriptyline in man is not known. It is not a monoamine oxidase inhibitor and it does not act primarily by stimulation of the central nervous system. In broad clinical use, amitriptyline has been found to be well tolerated.

Amitriptyline inhibits the membrane pump mechanism responsible for uptake of noradrenaline and serotonin in adrenergic and serotonergic neurons. Pharmacologically, this action may potentiate or prolong neuronal activity since reuptake of these biogenic amines is important physiologically in terminating its transmitting activity. This interference with the uptake of noradrenaline and/or serotonin is believed by some to underlie the antidepressant activity of amitriptyline.

Amitriptyline has also been found to be effective in the treatment of enuresis in some cases where organic pathology has been excluded. The mode of action of amitriptyline in enuresis is not known. However, amitriptyline does have anticholinergic properties and medicines of this group, such as belladonna, have been used in the treatment of enuresis.

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Amitriptyline is readily absorbed from the gastrointestinal tract, with peak plasma concentrations occurring within approximately 6 hours of oral administration.

Distribution

Amitriptyline is approximately 96% bound to plasma proteins.

Metabolism

Amitriptyline undergoes extensive metabolism in the liver, primarily through N-demethylation, to nortriptyline. Paths of metabolism of both amitriptyline and nortriptyline include hydroxylation and N-oxidation.

Excretion

The mean apparent elimination half-life for amitriptyline was reported by one source to be 22.4 hours; the mean half-life of its active metabolite, nortriptyline was 26 hours.

Amitriptyline is excreted in the urine, mainly in the form of metabolites, either free or as glucuronide and sulfate conjugates. Very little unchanged medicine is excreted in the urine. From one-third to one-half of an oral radioactive dose is excreted in the urine within 24 hours of administration.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Genotoxicity studies have not been performed with amitriptyline.

Carcinogenicity

Long-term carcinogenicity studies in rodents have not been performed with amitriptyline.

Accumulated data from up to 19 years follow-up in approximately 2,00 patients showed no statistically significant association between treatment with amitriptyline and the incidence of cancers. Clinical experience over 30 years has produced no evidence of an altered carcinogenic risk.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The 10 mg tablet contains lactose monohydrate, microcrystalline cellulose, disodium edetate, sodium starch glycollate, pregelatinised maize starch, colloidal anhydrous silica, purified talc, magnesium stearate and Opadry Blue OY-B-30904 (ID 3525).

The 25 mg tablet contains lactose monohydrate, microcrystalline cellulose, disodium edetate, sodium starch glycollate, pregelatinised maize starch, colloidal anhydrous silica, magnesium stearate and Opadry Yellow OY-LS-32814 (ID 2734).

The 50 mg tablet contains lactose monohydrate, microcrystalline cellulose, disodium edetate, sodium starch glycollate, pregelatinised maize starch, colloidal anhydrous silica, purified talc, magnesium stearate and Opadry Buff OY-LS-37200 (ID 3249).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

See Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

This medicinal product does not require any special storage conditions.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: Aluminium/PVC/PVDC blister packs and HDPE bottle (50 mg only).

Pack sizes:

10 mg tablet: available in blister packs of 50.

25 mg tablet: available in blister packs of 10, 50, 90 or 1000.

50 mg tablet: available in blister packs of 10, 50 or 1000 and bottles of 50.

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 71044 – ENDEP 10 amitriptyline hydrochloride 10mg tablet blister pack

AUST R 59788 – ENDEP 25 amitriptyline hydrochloride 25mg tablet blister pack

AUST R 64425 – ENDEP 50 amitriptyline hydrochloride 50mg tablet blister pack

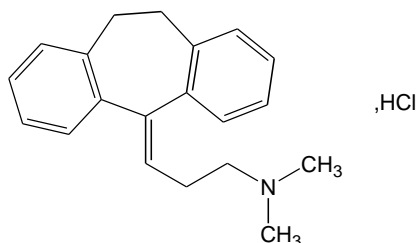
AUST R 64424 – ENDEP 50 amitriptyline hydrochloride 50mg tablet bottle

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure



Empirical formula: C₂₀H₂₃N.HCl

Molecular weight: 313.9

CAS Number

549-18-8

Amitriptyline hydrochloride occurs as colourless crystals or a white or almost white powder; odourless or almost odourless; taste, bitter and burning, followed by a sensation of numbness. It is soluble in 1 part of water, in 1.5 parts of ethanol (96%), in 1.2 parts of chloroform and in 1 part of methanol. It is practically insoluble in ether.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

Level 1, 30 The Bond

30 – 34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

ENDEP 10 blister pack: 20/09/1999

ENDEP 25 blister pack: 02/05/1997

ENDEP 50 blister pack & bottle: 19/05/1998

10 DATE OF REVISION

18/02/2025

Summary Table of Changes

Section Changed	Summary of New Information
-----------------	----------------------------

All	Minor editorial changes
4.4	Addition of severe cutaneous reactions.
4.8	Addition of SCARs including DRESS as an adverse effect.

ENDEP® is a Viartis company trade mark

ENDEP_pi\Feb25/00 (CCDS 30-Jun-2023)