

# AUSTRALIAN PRODUCT INFORMATION – ENTRIP (AMITRIPTYLINE HYDROCHLORIDE) TABLETS

## 1 NAME OF THE MEDICINE

Amitriptyline hydrochloride.

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ENTRIP tablets contain 10 mg, 25 mg or 50mg of amitriptyline hydrochloride.

Excipients with known effect: lactose monohydrate. For the full list of excipients, see **Section 6.1 LIST OF EXCIPIENTS**.

## 3 PHARMACEUTICAL FORM

ENTRIP 10 mg tablet: Round blue coloured biconvex tablets debossed AM on one side and 10 on the other side.

ENTRIP 25 mg tablet: Round yellow coloured biconvex tablets debossed AM on one side and 25 on the other side.

ENTRIP 50 mg tablet: Round brown coloured biconvex tablets debossed AM on one side and 50 on the other side.

## 4 CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

For the treatment of major depression. ENTRIP 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 amitriptyline hydrochloride 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)*

Amitriptyline 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, 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**

<b>Age Range</b>	<b>Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated</b>
<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 amitriptyline should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

### **Amitriptyline hydrochloride 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**

Amitriptyline 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 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 and Urinary Retention**

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

### **Cardiovascular Disorders**

Patients with cardiovascular disorders should be watched closely. Tricyclic antidepressant medicines, including amitriptyline, 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 Interactions with other medicines).

### **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 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 were changed immediately to protriptyline or vice versa.

### **Elective Surgery**

Discontinue the medicine several days before elective surgery if possible.

### **Impairment of Motor Co-ordination**

Amitriptyline may impair alertness in some patients; operation of motor vehicles and other activities made hazardous by diminished alertness should be avoided.

### **Use in hepatic impairment**

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

### **Use in the elderly**

See **Section 4.2 DOSE AND METHOD OF ADMINISTRATION**.

### **Paediatric use**

The safety and efficacy of amitriptyline for the treatment of depression or other psychiatric disorders in children and adolescents aged less than 18 years has not been satisfactorily established. Amitriptyline 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 amitriptyline (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 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 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).

#### **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 (i.e. levodopa) or which may be absorbed to a greater extent because of the increased time available for absorption (i.e. 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 or women who may become pregnant, 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**

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration. [optional]

## **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.

## **Cardiovascular**

Hypotension, syncope, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke, nonspecific ECG changes and changes in AV conduction.

## **Central nervous system and neuromuscular**

Confusional states, disturbed concentration, disorientation, delusions, hallucinations, excitement, anxiety, restlessness, insomnia, drowsiness, nightmares; numbness, tingling, paraesthesiae of the extremities, peripheral neuropathy, incoordination, ataxia, tremors, coma, seizures, alteration in EEG patterns, extrapyramidal symptoms including abnormal voluntary movements and tardive dyskinesia; dysarthria, tinnitus.

## **Anticholinergic**

Dry mouth, blurred vision, disturbance of accommodation, constipation, paralytic ileus, urinary retention, dilatation of urinary tract, increased intraocular pressure, hyperpyrexia.

## **Allergic**

Skin rash, urticaria, pruritus, photosensitisation, oedema of face and tongue.

## **Haematological**

Bone marrow depression including agranulocytosis, leucopenia, eosinophilia, purpura, thrombocytopenia.

## **Gastrointestinal**

Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhoea, parotid swelling, black tongue, rarely hepatitis (including altered liver function and jaundice).

## **Endocrine**

Testicular swelling and gynaecomastia in the male, breast enlargement and galactorrhoea in the female, increased or decreased libido, impotence, elevation or lowering of blood sugar levels, syndrome of inappropriate ADH (antidiuretic hormone) secretion.

## **Other**

Dizziness, weakness, fatigue, headache, weight gain or loss, oedema, increased perspiration, urinary frequency, mydriasis, drowsiness, alopecia.

## **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 amitriptyline 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](http://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**

High doses 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, convulsions, severe hypotension, stupor, coma and polyradiculoneuropathy. Changes in the electrocardiogram, particularly in QRS axis or width, are clinically significant indicators of tricyclic antidepressant toxicity. Other symptoms may be agitation, hyperactive reflexes, muscle rigidity, vomiting, hyperpyrexia, or any of those listed under Adverse Effects.

### **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 200 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**

ENTRIP tablets contain the following inactive excipients: lactose monohydrate, microcrystalline cellulose, maize starch, croscarmellose sodium, colloidal anhydrous silica, purified talc, magnesium stearate, hypromellose and Macrogol 6000. The tablet film coating contains OPADRY II complete film coating system 85F99075 BLUE (ARTG 109882 for 10 mg), 85F92349 YELLOW (ARTG 109879 for 25 mg) or 85F565015 BROWN (ARTG 109885 for 50 mg).

### **6.2 INCOMPATIBILITIES**

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

### **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 25°C. Protect from light.

### **6.5 NATURE AND CONTENTS OF CONTAINER**

ENTRIP 10 mg tablet: Available in PVC/PVDC/Al blister packs of 50 and 100 tablets; and HDPE bottles of 50, 250 and 1000 tablets.

ENTRIP 25 mg tablet: Available in PVC/PVDC/Al blister packs of 10, 50, 90, 100 and 1000 tablets; and HDPE bottles of 50, 250 and 1000 tablets.

ENTRIP 50 mg tablet: Available in PVC/PVDC/Al blister packs of 10, 50, 100 and 1000 tablets; and HDPE bottles of 50, 250 and 1000 tablets.

Not all pack sizes may be marketed.

### **6.6 SPECIAL PRECAUTIONS FOR DISPOSAL**

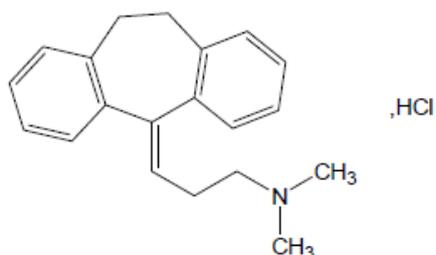
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

### **6.7 PHYSICOCHEMICAL PROPERTIES**

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.

#### **Chemical structure**

The chemical name for amitriptyline hydrochloride is 3-(10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-ylidene)-*N,N*-dimethylpropylamine hydrochloride. Its structural formula is:



Empirical formula:  $C_{20}H_{23}N.HCl$

Molecular weight: 313.9

**CAS number**

CAS Registry No.: 549-18-8

**7 MEDICINE SCHEDULE (POISONS STANDARD)**

S4 (Prescription Only Medicine)

**8 SPONSOR**

Arrow Pharma Pty Ltd  
 15-17 Chapel Street  
 Cremorne Victoria 3121

[www.arrowpharma.com.au](http://www.arrowpharma.com.au)

**9 DATE OF FIRST APPROVAL**

27 November 2015

**10 DATE OF REVISION**

14 December 2018

**SUMMARY TABLE OF CHANGES**

Section Changed	Summary of new information
All	Reformatting