NEW ZEALAND DATA SHEET

1. PRODUCT NAME
Arrow-Amitriptyline

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 10 mg, 25 mg or 50 mg of amitriptyline hydrochloride.

Excipient with known effect: lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Arrow-Amitriptyline 10mg tablets are blue coloured, circular biconvex film-coated tablets with "IA" embossed on one side and plain on the other side
10

Arrow-Amitriptyline 25mg tablets are yellow coloured, circular biconvex film-coated tablets with "IA" embossed on one side and plain on the other side.
25

Arrow-Amitriptyline 50mg tablets are brown coloured, circular biconvex film-coated tablets with "IA" embossed on one side and plain on the other side.
50

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Arrow-Amitriptyline is recommended for the treatment of depression.

4.2 Dose and method of administration
Dose

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

Adults
Outpatients
Initially, 75mg of amitriptyline a day in divided doses is usually satisfactory. If necessary, this may be increased to a total of 150mg 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 3 or 4 days or may take up to 30 days to develop adequately.

Alternate methods of initiating therapy in outpatients are to begin therapy with 50 to 100mg amitriptyline preferably in the evening or at bedtime; this may be increased by 25 to 50mg as necessary to a total of 150mg per day. Initiate therapy with one 75mg capsule or tablet preferably in the evening or at bedtime and increase, if necessary, to two, or one in the morning and one in the evening.

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

Special populations

Elderly Patients

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

Adolescent Depression

Not recommended for use in adolescent patients 13-18 years of age for the treatment of depression, unless under the supervision of a specialist.

Maintenance Dosage

The usual maintenance dose is 50 to 100mg amitriptyline 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.

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 noncompliance is suspected. Adjustments in dosage should be made according to the patient's clinical response and not on the basis of plasma levels.

Method of administration

For oral administration.

4.3 Contraindications

- Amitriptyline is contraindicated for the treatment of depression in patients 12 years of age and under.
- Amitriptyline is contraindicated for the treatment of nocturnal enuresis.
- Amitriptyline is contraindicated in patients who have shown prior hypersensitivity to it.
- It should not be given concomitantly with a monoamine oxidase inhibiting compound. Hyperpyretic crises, severe convulsions, and deaths have occurred in patients receiving tricyclic antidepressant and monoamine oxidase inhibiting medicines simultaneously. 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.
- Amitriptyline is contraindicated during the acute recovery phase following myocardial infarction.
- See section 4.6 Fertility, pregnancy and lactation.

4.4 Special warnings and precautions for use

Clinical Worsening and Suicide Risk

Patients of any age with Major Depressive Disorder may experience worsening of their depression 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. Patients should be closely monitored, especially at the beginning of therapy or when the dose is changed, until such improvement occurs.

There has been a long-standing concern that some antidepressants may have a role in the emergence of suicidality in some patients. The possible risk of increased suicidality in patients applies to all classes of antidepressant medicines, as available data are not adequate to exclude this risk for any

antidepressant. Therefore, 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. Generally, when stopping an antidepressant, doses should be tapered rather than stopped abruptly.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and paediatric patients 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 the worsening of depression and/or the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and non-psychiatric disorders, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric and non-psychiatric disorders.

Mania and Bipolar Disorder
A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with any antidepressant alone may increase the likelihood of a mixed/manic episode in patients at risk for bipolar disorder. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder. It should be noted that amitriptyline is not approved for use in treating bipolar depression.

Information for Patients and Families
Patients and their families should be alerted about the need to monitor for the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, mania, worsening of depression, and suicidal ideation, especially early during antidepressant treatment. Such symptoms should be reported to the patient's doctor, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

The patient has the right to treatment meeting appropriate ethical and professional standards, and the patient needs to be fully informed with frank discussion of risk/benefit issues relating to the medicines efficacy and safety when used in the treatment regimen proposed.

General
Amitriptyline should be used with caution in patients with a history of seizures, in patients with impaired liver function and, because of its atropine-like action, 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 may precipitate an attack.

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

Discontinue the medicine several days before elective surgery if possible.

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

The medicine may impair alertness in some patients; operation of automobiles and other activities made hazardous by diminished alertness should be avoided.

Cardiovascular Disorders
Amitriptyline should be used with caution in patients with cardiovascular disease, including heart failure, conduction disorders, (e.g. AV block grades I to III), or arrhythmias. Cardiovascular and ECG monitoring should be undertaken in such patients. An ECG should be performed prior to starting treatment, at steady state, after an increase in dose or after starting any potentially interacting medicine.

Tricyclic antidepressant medicines, including amitriptyline particularly when given in high doses, have been reported to produce QTc prolongation, arrhythmias (including torsades de points (TdP), sinus tachycardia, and prolongation of the conduction time). Myocardial Infarction and stroke have been reported with medicines of this class (see section 4.8 Undesirable effects).

Amitriptyline should be used with caution in patients with risk factors for QTc prolongation/TdP including congenital long QT syndrome, age >65 years, female sex, structural heart disease/LV dysfunction, medical conditions such as renal or hepatic disease, use of medicines that inhibit the metabolism of amitriptyline, and the concomitant use of other QTc prolonging medicines (see section 4.5 Interaction with other medicines and other forms of interaction). Hypokalaemia and hypomagnesaemia should be corrected prior to treatment.

Consideration should be given to stopping amitriptyline treatment or reducing the dose if the QTc interval is >500ms or increases by >60ms.

Endocrine Disorders
Close supervision is required when amitriptyline is given to hyperthyroid patients or those receiving thyroid medication.

Central Nervous System Disorders
When amitriptyline is used to treat the depressive component of schizophrenia, psychotic symptoms may be aggravated.

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.

4.5 Interaction with other medicines and other forms of interaction

Sympathomimetic agents: Amitriptyline may potentiate the cardiovascular effects of adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine, and phenylpropanolamine (e.g. as contained in local and general anaesthetics and nasal decongestants).

Adrenergic neurone blockers: Tricyclic antidepressants may counteract the antihypertensive effects of centrally acting antihypertensives such as guanethidine, betanidine, reserpine, clonidine and methyldopa. It is advisable to review all antihypertensive therapy during treatment with tricyclic antidepressants.

Anticholinergic agents: Tricyclic antidepressants may potentiate the effects of these drugs on the eye, central nervous system, bowel and bladder; concomitant use of these should be avoided due to an increased risk of paralytic ileus, hyperpyrexia, etc.

Amitriptyline for enuresis should not be combined with an anticholinergic drug.[3]

Medicines that can prolong the QTc interval: The risk of QTc prolongation and/or ventricular arrhythmias (e.g. torsades de pointes) is increased with concomitant use of other medicines which prolong the QTc interval (e.g. some antipsychotics and antibiotics). Please check the data sheet of other medicines administered for information on their effects on the QT interval.

Use caution when using amitriptyline and methadone concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects.

Caution is also advised for co-administration of amitriptyline and diuretics inducing hypokalaemia (e.g. furosemide)

Thioridazine: Co-administration of amitriptyline and thioridazine (CYP2D6 substrate) should be avoided due to inhibition of thioridazine metabolism and consequently increased risk of cardiac side effects.

Tramadol: Concomitant use of tramadol (a CYP2D6 substrate) and tricyclic antidepressants (TCAs), such as amitriptyline increases the risk for seizures and serotonin syndrome. Additionally, this combination can inhibit the metabolism of tramadol to the active metabolite and thereby increasing tramadol concentrations potentially causing opioid toxicity.

Antifungals such as fluconazole and terbinafine increase serum concentrations of tricyclics and accompanying toxicity. Syncope and torsade de pointes have occurred.

Combinations requiring precautions for use

CNS depressants: Amitriptyline may enhance the sedative effects of alcohol, barbiturates and other CNS depressants.

Potential of other medicinal products to affect amitriptyline
Tricyclic antidepressants (TCA) including amitriptyline are primarily metabolised by the hepatic cytochrome P450 isozymes CYP2D6 and CYP2C19, which are polymorphic in the population. Other isozymes involved in the metabolism of amitriptyline are CYP3A4, CYP1A2 and CYP2C9.

CYP2D6 inhibitors: The CYP2D6 isozyme can be inhibited by a variety of drugs, e.g. neuroleptics, serotonin reuptake inhibitors, beta blockers, and antiarrhythmics. Examples of strong CYP2D6 inhibitors include bupropion, fluoxetine, paroxetine and quinidine. These drugs may produce substantial decreases in TCA metabolism and marked increases in plasma concentrations. Consider to monitor TCA plasma levels, whenever a TCA is to be co-administered with another drug known to be an inhibitor of CYP2D6. Dose adjustment of amitriptyline may be necessary (see section "Posology and method of administration").

Other Cytochrome P450 inhibitors: Cimetidine, methylphenidate and calcium-channel blockers (e.g. diltiazem and verapamil) may increase plasma levels of tricyclic antidepressants and accompanying toxicity. Antifungals such as fluconazole (CYP2C9 inhibitor) and terbinafine (CYP2D6 inhibitor) have been observed to increase serum levels of amitriptyline and nortriptyline.

The CYP3A4 and CYP1A2 isozymes metabolise amitriptyline to a lesser extent. However, fluvoxamine (strong CYP1A2 inhibitor) was shown to increase amitriptyline plasma concentrations and this combination should be avoided. Clinically relevant interactions may be expected with concomitant use of amitriptyline and strong CYP3A4 inhibitors such as ketoconazole, itraconazole and ritonavir.

Tricyclic antidepressants and neuroleptics mutually inhibit the metabolism of each other; this may lead to a lowered convulsion threshold, and seizures. It may be necessary to adjust the dosage of these drugs.

Cytochrome P450 inducers: Oral contraceptives, rifampicin, phenytoin, barbiturates, carbamazepine and St. John's Wort (Hypericum perforatum) may increase the metabolism of tricyclic antidepressants and result in lowered plasma levels of tricyclic antidepressants and reduced antidepressant response.

In the presence of ethanol amitriptyline free plasma concentrations and nortriptyline concentrations were increased.

Amitriptyline plasma concentration can be increased *by sodium valproate and valpromide*. Clinical monitoring is therefore recommended.

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.

4.6 Fertility, pregnancy and lactation

Use in pregnancy (Category C)
For amitriptyline, only limited clinical data are available regarding exposed pregnancies. Animal studies have shown reproductive toxicity. Amitriptyline is not recommended during pregnancy unless clearly necessary and only after careful consideration of the risk/benefit.

During chronic use and after administration in the final weeks of pregnancy, neonatal withdrawal symptoms can occur. This may include irritability, hypertonia, tremor, irregular breathing, poor drinking and loud crying and possibly anticholinergic symptoms (urinary retention, constipation).

Lactation
Amitriptyline and its metabolites are excreted into breast milk (corresponding to 0.6 % - 1 % of the maternal dose). A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from the therapy of this medicinal product taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility
Amitriptyline reduced the pregnancy rate in rats. No data on the effects of amitriptyline on human fertility are available.

4.7 Effects on ability to drive and use machines

Amitriptyline is a sedative medicine. Patients who are prescribed psychotropic medication may be expected to have some impairment in general attention and concentration and should be cautioned about their ability to drive or operate machinery. These adverse effects can be potentiated by the concomitant intake of alcohol.

4.8 Undesirable effects

Summary of the safety profile
Amitriptyline may induce side effects similar to other tricyclic antidepressants. Some of the below mentioned side effects e.g. headache, tremor, disturbance in attention, constipation and decreased libido may also be symptoms of depression and usually attenuate when the depressive state improves.

Cardiovascular effects
Hypotension, syncope, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias (including ventricular tachycardia, ventricular fibrillation and Torsades de Pointes, stroke, ECG changes (including QTc prolongation, non-specific ST and T wave changes, and AV conduction disorders such as heart block, bundle branch block and widened QRS complex).

List of adverse reactions
The frequencies of adverse events are ranked according to the following: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

Blood and lymphatic system disorders

Rare:	Bone marrow depression, agranulocytosis, leucopenia, eosinophilia, thrombocytopenia

Metabolism and nutrition disorders

Rare:	Decreased appetite
Not known:	Anorexia, elevation or lowering of blood sugar levels

Psychiatric disorders

Very common:	Aggression
Common:	Confusional state, libido decreased, agitation
Uncommon:	Hypomania, mania, anxiety, insomnia, nightmare
Rare:	Delirium (in elderly patients), hallucination, suicidal thoughts or behaviour*
Not known:	Paranoia

Nervous system disorders

Very common:	Somnolence, tremor, dizziness, headache, drowsiness, speech disorder (dysarthria)
Common:	Disturbance in attention, dysgeusia, paresthesia, ataxia
Uncommon:	Convulsion
Very rare:	Akathisia, polyneuropathy
Not known:	Extrapyramidal disorder

Eye disorders

Very common:	Accommodation disorder
Common:	Mydriasis
Very rare:	Acute glaucoma
Not known:	Dry eye

Ear and labyrinth disorders

Uncommon:	Tinnitus

Cardiac disorders

Very common:	Palpitations, tachycardia
Common:	Atrioventricular block, bundle branch block
Uncommon:	Collapse conditions, worsening of cardiac failure
Rare:	Arrhythmia
Very rare:	Cardiomyopathies, Torsade de pointes
Not known:	Hypersensitivity myocarditis

Vascular disorders

Very common:	Orthostatic hypotension
Uncommon:	Hypertension
Not known:	Hyperthermia

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, tongue oedema
Rare:	Salivary gland enlargement, ileus paralytic

Hepatobiliary disorders

Uncommon:	Hepatic impairment (e.g. cholestatic liver disease)
Rare:	Jaundice
Not known:	Hepatitis

Skin and subcutaneous tissue disorders

Very common:	Hyperhidrosis
Uncommon:	Rash, urticaria, face oedema
Rare:	Alopecia, photosensitivity reaction

Renal and urinary disorders

Common:	Micturition disorders
Uncommon:	Urinary retention

Reproductive system and breast disorders

Common:	Erectile dysfunction
Uncommon:	Galactorrhoea
Rare:	Gynaecomastia

General disorders and administration site conditions

Common:	Fatigue, feeling thirst
Rare:	Pyrexia

Investigations

Very common:	Weight increased
Common:	Electrocardiogram abnormal, electrocardiogram QT prolonged, electrocardiogram QRS complex prolonged, hyponatremia
Uncommon:	Intraocular pressure increased
Rare:	Weight decreased, liver function test abnormal, blood alkaline phosphatase increased, transaminases increased

*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).

Class effects

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

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 symptoms are not indicative of addiction. Rare instances have been reported of mania or hypomania occurring within 2-7 days following cessation of chronic therapy with tricyclic antidepressants.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Symptoms
Anticholinergic symptoms: Mydriasis, tachycardia, urinary retention, dry mucous membranes, reduced bowel motility, convulsions, fever, sudden occurrence of CNS depression, lowered consciousness progressing into coma, respiratory depression.

Cardiac symptoms: Arrhythmias (ventricular tachyarrhythmias, Torsade de pointes, ventricular fibrillation). The ECG characteristically show 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. Widening of the QRS-complex usually correlates well with the severity of the toxicity following acute overdoses. Heart failure, hypotension, cardiogenic shock, metabolic acidosis, hypokalemia, hyponatraemia[7].

Ingestion of 750 mg or more by an adult may result in severe toxicity. The effects in overdose will be potentiated by simultaneous ingestion of alcohol and other psychotropic. There is considerably individual variability in response to overdose.

Children are especially susceptible to cardiotoxicity, seizures and hyponatraemia.

During awakening possibly again confusion, agitation and hallucinations and ataxia.

Treatment
1. Admission to hospital (intensive care unit) if required. Treatment is symptomatic and supportive.
2. Assess and treat ABC's (airway, breathing and circulation) as appropriate. Secure an IV access. Close monitoring even in apparently uncomplicated cases.
3. Examine for clinical features. Check urea and electrolytes -look for low potassium and monitor urine output. Check arterial blood gases - look for acidosis. Perform electrocardiograph - look for QRS>0.16 seconds
4. Do not give flumazenil to reverse benzodiazepine toxicity in mixed overdoses.
5. Consider gastric lavage only if within one hour of a potentially fatal overdose.
6. Give 50 g of charcoal if within one hour of ingestion.
7. Patency of the airway is maintained by intubation, where required. Treatment in respirator is advised to prevent a possible respiratory arrest. Continuous ECG-monitoring of cardiac function for 3-5 days. Treatment of the following will be decided on a case by case basis:

- Wide QRS-intervals, cardiac failure and ventricular arrhythmias
- Circulatory failure
- Hypotension
- Hyperthermia
- Convulsions
- Metabolic acidosis.

8. Unrest and convulsions may be treated with diazepam.

9. Patients who display signs of toxicity should be monitored for a minimum of 12 hours.

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

11. 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidepressants, nonselective monoamine reuptake inhibitors, ATC code: N06AA09

Amitriptyline is a potent antidepressant with sedative properties. The mechanism of action in humans 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 norepinephrine 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 transmitting activity. This interference with the reuptake of norepinephrine and/or serotonin is believed by some to underlie the antidepressant activity of amitriptyline.

5.2 Pharmacokinetic properties

Absorption

Appears in plasma within 30 to 60 minutes after oral ingestion and 5 to 10 minutes after intramuscular injection. Approximately 62% of the radioactive doses of C_{14} was recovered in human urine after oral or intravenous administration. Plasma levels are very low with broad peaks ranging from 2-12 hours after administration.

Metabolism

In one study, 12 normal subjects received 25mg of amitriptyline t.i.d. plasma amitriptyline levels were maximal (62 ± 20 ng/ml) at 4 hours post therapy. In another study in which 12 normal subjects received 25mg amitriptyline t.i.d. for 2 weeks, the plasma half-life averaged 30 hours.

Studies in humans following oral administration of ^{14}C-labelled medicine indicated that amitriptyline is rapidly absorbed and metabolised. Radioactivity of the plasma was practically negligible, although significant amounts of radioactivity appeared in the urine by 4 to 6 hours and one-half to one-third of the medicine was excreted within 24 hours.

Amitriptyline is metabolised by N-demethylation and bridge hydroxylation in humans, rabbit, and rat. Virtually the entire dose is excreted as glucuronide or sulphate conjugate of metabolites, with little unchanged medicine appearing in the urine. Other metabolic pathways may be involved.

Excretion

Urine

Following an intravenous dose, an average total of 62.9% of radioactivity was excreted in 7 days, with 25.1% being excreted in the first 24 hours. Following oral administration, an average total of 63.0% of radioactivity was excreted in 7 days, with 27.0% excreted in the first 24 hours.

Faeces

Following oral administration C_{14}-labelled tablets, excretion of radioactivity was calculated to be 10.5% (average) over 7 days; after intravenous administration, an average of 12.7% was recovered in the faeces in 7 days.

Bile

Animal studies show that amitriptyline and its metabolites are excreted in the bile.

Milk

In one report, following 100 mg/day of oral amitriptyline, levels of 135-151 ng/ml were found in the breast milk of a lactating patient.

5.3 Preclinical safety data

No information available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core

Lactose monohydrate, microcrystalline cellulose, crospovidone, maize starch, silica, talc, magnesium stearate.

Film coating

Brilliant blue FCF Al lake E133 (10mg), Quinoline yellow Aluminium lake E104 (25mg), Sunset yellow FCF aluminium lake E 110, Indigo carmine aluminium lake E 132 (50 mg), hypromellose, talc, titanium dioxide, macrogol 6000.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 25°C. Protect from light and moisture.

6.5 Nature and contents of container

PVC/Aluminium foil blister strips. Pack sizes of 30, 50 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Teva Pharma (New Zealand) Limited
PO Box 128 244
Remuera
Auckland 1541
Telephone: 0800 800 097

9. DATE OF FIRST APPROVAL

1 March 2012

10. DATE OF REVISION OF THE TEXT

28 May 2019

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.5, 4.6, 4.7, 4.8, 4.9	Updated safety information in accordance with Teva CCSI No. 116/10/10/18