Approved Professional Information for Medicines for Human Use:

AMITRIPTYLINE 10 mg AUSTELL

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

AMITRIPTYLINE 10 mg AUSTELL film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains amitriptyline hydrochloride 10 mg equivalent to amitriptyline 8,84 mg.

Contains sugar.

Each AMITRIPTYLINE 10 mg AUSTELL film-coated tablet contains 48,95 mg lactose monohydrate equivalent to 46,5 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

AMITRIPTYLINE 10 mg AUSTELL tablets are blue coloured, circular, biconvex, film-coated tablets with “IA” over “10” debossed on one side and plain on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Depression

Amitriptyline is a tricyclic antidepressant used in the treatment of patients with endogenous depression. It possesses mild tranquillising and sedative properties which are helpful in alleviating anxiety or agitation that often accompany depression. It has been used with benefit in depression of long or short duration.

Nocturnal enuresis

Adjunctive therapy for nocturnal enuresis in children over 6 years of age where organic pathology has been excluded.

4.2 Posology and method of administration

Posology

Depression

Adults

Initial

25 mg three times per day increasing gradually to 150 mg daily if necessary.

Additional doses should be taken in the late afternoon or evening. Therapy may also be initiated with a single dose of 50 to 100 mg at night increased by 25 or 50 mg as necessary to a total of 150 mg daily. The antidepressant activity may be evident within three or four days or may take up to 30 days to develop adequately.

Maintenance

50 mg to 100 mg daily.

Treatment should be continued for at least three months before being gradually withdrawn (see sections 4.4 and 4.8). Hospitalized patients may be given doses of up to 200 mg daily and, occasionally, up to 300 mg daily.

Nocturnal enuresis

Children 6 to 10 years: 10 mg to 20 mg at bedtime.

Children 11 to 16 years: 25 mg to 50 mg at bedtime.

Do not exceed the recommended dose. Treatment should not be continued for longer than 3 months.

4.3 Contraindications

- Hypersensitivity to amitriptyline or any of the excipients listed in section 6.1.
- Concomitant treatment with MAOIs (monoamine oxidase inhibitors) (see section 4.5). 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 10 mg AUSTELL for a monoamine oxidase inhibitor, a minimum of 14 days should be allowed to elapse after the latter is discontinued. AMITRIPTYLINE 10 mg AUSTELL should then be initiated cautiously with gradual increases in doses until optimum response is achieved.
- Concomitant treatment with antihypertensive medicine, particularly adrenergic blocking medicines (see section 4.5).
- The immediate recovery/acute-phase of myocardial infarction and in patients with any degree of heart block or disorders of cardiac rhythm and coronary artery insufficiency as dysrhythmias, sinus tachycardia and prolongation of conduction time have been reported.
- Concomitant treatment with cisapride due to the possibility of adverse cardiac interactions including prolongation of the QT interval, cardiac dysrhythmias and conduction system disturbances.
- Treatment of depression in children under 12 years of age (see sections 4.2 and 4.4).

- Treatment of nocturnal enuresis in children under 6 years of age (see sections 4.2 and 4.4).
- Lactation.
- Severe liver disease (see section 4.4).
- Mania (see section 4.4).
- Administration of AMITRIPTYLINE 10 mg AUSTELL is not advised during the first trimester of pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

This medicine should at all times be kept out of the reach of children, as even small doses may be fatal to them.

Clinical worsening and suicide risk associated with psychiatric disorders

Patients with suicidal tendencies should be carefully supervised during treatment.

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 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.

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

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

Caution should be exercised with patients suffering from a depressive phase of manic-depressive psychosis, as tricyclic antidepressants such as AMITRIPTYLINE 10 mg AUSTELL may occasionally precipitate hypomania or mania in such patients. Withdraw AMITRIPTYLINE 10 mg AUSTELL if the depression turns into a manic phase.

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

Epilepsy may be aggravated. AMITRIPTYLINE 10 mg AUSTELL should be used with caution in patients with a history of seizures.

Central nervous system 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, AMITRIPTYLINE 10 mg AUSTELL should be used with caution in patients with narrow angle glaucoma or increased intraocular pressure. In patients with the rare condition of shallow anterior chamber and narrow chamber angle, attacks of acute glaucoma due to dilation of the pupil may be provoked. In patients with narrow angle glaucoma, even average doses precipitate an attack.

Cardiovascular disorders

In patients with cardiovascular disorders special caution should be observed. Tricyclic antidepressant medicines, such as AMITRIPTYLINE 10 mg AUSTELL, particularly when given in high doses, have been reported to produce severe hypotension, dysrhythmias, sinus tachycardia, prolongation of the conduction time and electrocardiographic

abnormalities. Myocardial infarction and stroke have been reported with medicines of this class. These undesirable effects may also occur in patients with pre-existing heart disease taking normal dosage. Regular cardiological and electrocardiographic examination is advised.

QT interval prolongation

Cases of QT interval prolongation and dysrhythmia have been reported during the post-marketing period. Caution is advised in patients with significant bradycardia, in patients with uncompensated heart failure, or in patients concurrently taking QT-prolonging drugs. Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) are known to be conditions increasing the prodysrhythmic risk.

Endocrine disorders

Use in diabetic patients

As described for other psychotropics, amitriptyline may modify insulin and glucose responses calling for adjustment of the antidiabetic therapy in diabetic patients; in addition, the depressive illness itself may affect patients' glucose balance.

Use in hyperthyroid and hypothyroid patients

Great care is necessary if amitriptyline is administered to hyperthyroid patients or to those receiving thyroid medication, since cardiac dysrhythmias may develop (see section 4.5).

Porphyria

The use of AMITRIPTYLINE 10 mg AUSTELL in patients suffering from acute forms of porphyria, especially variegate porphyria and to a lesser extent acute intermittent

porphyria and hereditary coproporphyria, is contentious, and thus AMITRIPTYLINE 10 mg AUSTELL should be used with caution in these patients.

Other disorders

AMITRIPTYLINE 10 mg AUSTELL should be used with caution in patients with urinary retention, prostatic hypertrophy, advanced hepatic disease, constipation, pylorus stenosis and paralytic ileus.

Concomitant use with 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.

Amitriptyline should be used with caution in patients receiving SSRIs due to the risk of "serotonin syndrome" (see sections 4.5 and 4.8).

Elective surgery

AMITRIPTYLINE 10 mg AUSTELL enhances the pressor effects of direct-acting sympathomimetic medicines, such as epinephrine (adrenaline) and nor-epinephrine (noradrenaline). Local anaesthetics containing these vasoconstrictors should be avoided as hypertensive reactions may occur. When possible, treatment with AMITRIPTYLINE 10 mg AUSTELL should be discontinued several days before elective surgery. In addition,

the hypotensive effect of certain antihypertensive medicines may be reduced (see section 4.5).

Anaesthetics given during tri/tetracyclic antidepressant therapy may increase the risk of dysrhythmias and hypotension. If possible, discontinue this medicine several days before surgery; if emergency surgery is unavoidable, the anaesthetist should be informed that the patient is being so treated.

Allergic skin reactions

Withdraw AMITRIPTYLINE 10 mg AUSTELL immediately if allergic skin reactions appear.

Anticholinergic effects

Due to its atropine-like action, AMITRIPTYLINE 10 mg AUSTELL may cause peripheral anticholinergic side effects, notably dry mouth, constipation, urinary retention and pupillary dilatation with blurred vision and changes in visual accommodation may occur. AMITRIPTYLINE 10 mg AUSTELL should be used with caution in patients with a history of urinary retention. When anticholinergic effects are severe, AMITRIPTYLINE 10 mg AUSTELL should be discontinued or reduced (see sections 4.8 and 4.9)

Concomitant use with MAOIs (monoamine oxidase inhibitors)

Concomitant treatment with MAOIs is contraindicated as it may cause serotonin syndrome (see sections 4.3 and 4.5).

Treatment with amitriptyline after discontinuation of MAOIs or treatment with MAOIs after discontinuation of amitriptyline may be instituted only after 14 days has elapsed (see section 4.3)

Concomitant use with anticholinergic or with neuroleptic medicines

The simultaneous administration of anticholinergic or neuroleptic medicines may be dangerous. Hyperpyrexia has been reported with tricyclic antidepressants when administered with anticholinergic or with neuroleptic medications, especially in hot weather (see section 4.5).

Concomitant use with central nervous system depressants

Drowsiness or excessive sedation may be caused in certain patients. On the other hand, disorientation and agitation, insomnia and restlessness can also occur with normal doses. The risks of central nervous system depression are greater when administered together with other central nervous system depressants, e.g. alcohol, barbiturates (see section 4.5).

Central nervous system depressants including alcohol and anticholinergic medicines can have their effects increased by AMITRIPTYLINE 10 mg AUSTELL.

AMITRIPTYLINE 10 mg AUSTELL should not usually be given to patients receiving other central nervous system depressants, and only after a suitable interval has elapsed (the medicines may be given together if the dosages are carefully controlled, preferably in hospital).

Concomitant use with antihypertensive agents

The hypotensive effect of certain antihypertensive agents may be reduced (see section 4.5).

Withdrawal

After prolonged administration, abrupt cessation of therapy may produce withdrawal symptoms such as headache, malaise, insomnia and irritability (see sections 4.2 and 4.8).

Nocturnal enuresis

An ECG should be performed prior to initiating therapy with amitriptyline to exclude long QT syndrome.

Amitriptyline for enuresis should not be combined with an anticholinergic medicine.

Suicidal thoughts and behaviours may also develop during early treatment with antidepressants for disorders other than depression; the same precautions observed when treating patients with depression should therefore be followed when treating patients with enuresis.

Impairment of alertness and motor co-ordination

AMITRIPTYLINE 10 mg AUSTELL may impair alertness and motor co-ordination in some patients (see sections 4.7 and 4.8).

At the time of initiation of therapy, patients should be advised not to drive a motor vehicle, climb dangerous heights or operate dangerous machinery for at least several days. In these situations, impaired decision making could lead to accidents.

Elderly population

Elderly patients are particularly susceptible to orthostatic hypotension that may be caused by AMITRIPTYLINE 10 mg AUSTELL.

In elderly male patients suffering from prostatism, urinary retention may be precipitated.

Elderly patients are more prone to all the undesirable effects caused by tricyclic antidepressants such as AMITRIPTYLINE 10 mg AUSTELL, e.g. drowsiness or excessive sedation, disorientation and agitation, insomnia and restlessness. Therapy should be initiated at lower than standard doses in the elderly. See section 4.8.

Paediatric population

Long-term safety data in children and adolescents aged less than 18 years concerning growth, maturation and cognitive and behavioural development are not available. AMITRIPTYLINE 10 mg AUSTELL should not be used in this age group for the treatment of depression.

Excipient lactose

AMITRIPTYLINE 10 mg AUSTELL tablets contain lactose. Patients with the rare hereditary conditions of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take AMITRIPTYLINE 10 mg AUSTELL.

4.5 Interaction with other medicines and other forms of interaction

Potential for amitriptyline to affect other medicines

Contraindicated combinations

Monoamine oxidase inhibitors (MAOIs)

A potentially lethal interaction due to “serotonin syndrome” can occur between tricyclic antidepressants and MAOIs (non-selective as well as selective MAOI-A [moclobemide] and selective MAOI-B [selegiline]). It is advisable to discontinue the MAOI for at least 2 weeks before taking AMITRIPTYLINE 10 mg AUSTELL (see section 4.3).

Cisapride

Amitriptyline, as in AMITRIPTYLINE 10 mg AUSTELL is contraindicated in patients taking cisapride due to the possibility of adverse cardiac interactions including prolongation of the QT interval, cardiac dysrhythmias and conduction system disturbances (see section 4.3).

Combinations that are not recommended

Sympathomimetic medicines

Amitriptyline may potentiate the cardiovascular effects of adrenaline (epinephrine), ephedrine, isoprenaline, noradrenaline (norepinephrine), phenylephrine, and phenylpropanolamine (e.g. as contained in local and general anaesthetics and nasal decongestants) and hypertensive reactions may occur. When possible, treatment should be discontinued several days before elective surgery.

Adrenergic neurone blockers

Tricyclic antidepressants may counteract the antihypertensive effects of centrally acting antihypertensives such as guanethidine, betanidine, reserpine, clonidine and methyldopa (see section 4.4). Concurrent use of antihypertensive adrenergic blocking medicines such as guanethidine and AMITRIPTYLINE 10 mg AUSTELL is contraindicated (see section 4.3).

Anticholinergic medicines

Tricyclic antidepressants may potentiate the effects of these medicines 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.

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 dysrhythmias and CNS stimulation.

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.

Medicines which prolong the QT-interval

The likelihood of ventricular dysrhythmias may increase when taking tricyclic antidepressants with medicines which prolong the QT-interval including antidysrhythmics such as amiodarone or quinidine (avoid concomitant use), disopramide, procainamide, propafenone, the antihistamines astemizole and terfenadine, some antipsychotics (notably pimozide, thioridazine and sertindole), cisapride, halofantrine and sotalol. This effect may be exacerbated where the interacting medicine (such as quinidine or some

antipsychotics) also reduces the metabolism of amitriptyline. Caution is advised during concurrent use with AMITRIPTYLINE 10 mg AUSTELL.

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).

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).

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

The serum concentrations of tricyclics and accompanying toxicity is increased by antifungals such as fluconazole and terbinafine. Syncope and torsade de pointes have occurred.

Guanethidine

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

Combinations requiring precautions for use

CNS depressants

Amitriptyline may enhance the sedative effects of alcohol, barbiturates and other CNS depressants. AMITRIPTYLINE 10 mg AUSTELL should not usually be given to patients receiving other central nervous system depressants - only after a suitable interval has elapsed (the medicines may be given together if the dosages are carefully controlled, preferably in hospital) (see section 4.4).

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).

Potential of other medicines to affect amitriptyline

Cytochrome inhibitors and inducers

Tricyclic antidepressants (TCA) including amitriptyline are primarily metabolised by the hepatic cytochrome P450 isozymes CYP2D6 and CYP2C19, which are polymorphic in the population (see section 4.2). 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 antidysrhythmics. 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 monitoring 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 4.2).

Other cytochrome P450 inhibitors

Cimetidine, antipsychotics, antivirals, 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

When used simultaneously, amitriptyline 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 medicines.

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.

Alpha2-adrenoceptor stimulants

Concomitant use of apraclonidine and brimonidine should be avoided.

Altretamine

Risk of severe postural hypotension.

Anaesthetics

Concomitant therapy may increase the risk of dysrhythmias and hypotension. If surgery is necessary, the anaesthetist should be informed that a patient is being so treated (see section 4.4).

Analgesics

There is a possibility of increased side effects with nefopam. There is a possibility of increased sedation with opioid analgesics.

Antibacterials

Concomitant use with linezolid may result in CNS excitation and hypertension.

Anxiolytics and hypnotics

Concomitant use enhances the sedative effect. Caution is advised if patients receive large doses of ethchlorvynol concurrently. Transient delirium has been reported in patients treated with 1 g ethchlorvynol and 75 mg to 150 mg of amitriptyline.

Cimetidine

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

Disulfiram

Concomitant use may inhibit the metabolism of tricyclics. Delirium has been reported in patients taking amitriptyline with disulfiram.

Diuretics

Increased risk of postural hypotension.

Dopaminergics

Concomitant use with entacapone should be avoided. CNS toxicity has been reported with selegiline.

Estrogens and progestogens

Oral contraceptives antagonise the antidepressant effect, but side-effects may be increased due to increased plasma concentrations of tricyclics.

Muscle relaxants

Concomitant use of baclofen enhances its muscle relaxant effect.

Nitrates

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

Other antidepressant medicines

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.

Sibutramine

Concomitant use is not recommended due to the increased risk of CNS toxicity.

Sodium valproate and valpromide

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

4.6 Fertility, pregnancy and lactation

Fertility

No data on the effects of amitriptyline on human fertility are available.

Pregnancy

Safety of AMITRIPTYLINE 10 mg AUSTELL during pregnancy has not been established. Administration of AMITRIPTYLINE 10 mg AUSTELL is not advised during the first trimester of pregnancy unless there are compelling reasons for its use (see section 4.3).

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).

Breastfeeding

Safety of AMITRIPTYLINE 10 mg AUSTELL during lactation has not been established (see section 4.3).

AMITRIPTYLINE 10 mg AUSTELL is contraindicated in breastfeeding.

4.7 Effects on ability to drive and use machines

[PROCUCT NAME] may cause drowsiness, dizziness, disturbance of vision and impairment of alertness and motor co-ordination in some patients, especially at the beginning of treatment.

Patients should be instructed not to drive a motor vehicle, climb dangerous heights, operate machinery and/or undertake activities that may be hazardous by diminished alertness if they are affected by [PROCUCT NAME]. These adverse effects can be potentiated by the concomitant intake of alcohol.

4.8 Undesirable effects

a. Summary of the safety profile

The following side effects have been reported with use of AMITRIPTYLINE 10 mg AUSTELL. Many of the side effects of AMITRIPTYLINE 10 mg AUSTELL are related to its anticholinergic actions, notably dry mouth, constipation, urinary retention and pupillary dilatation with blurred vision and changes in visual accommodation. When anticholinergic effects are severe, AMITRIPTYLINE 10 mg AUSTELL should be discontinued or reduced.

b. Tabulated summary of adverse reactions

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
Blood and lymphatic system disorders		bone marrow depression, agranulocytosis, leucopenia, eosinophilia, thrombocytopenia, purpura	

Metabolism and nutrition disorders		decreased appetite	elevation or lowering of blood sugar levels, increased appetite, anorexia.
Psychiatric disorders	aggression, confusional state, libido decreased, agitation	hypomania, mania, anxiety, insomnia, nightmares, delirium (in elderly patients), hallucinations, suicidal thoughts or behaviour*	paranoia
Nervous system disorders	somnolence, tremor, dizziness, headache, drowsiness,	convulsion, akathisia, polyneuropathy	weakness, disturbed concentration, disorientation, delusions, excitement,

	speech disorder (dysarthria), disturbance in attention, dysgeusia, paresthesia, ataxia		restlessness, numbness, tingling, peripheral neuropathy, inco-ordination, coma, seizures, alteration in EEG patterns, extrapyramidal disorder including speech difficulties, abnormal voluntary movements and tardive dyskinesia
Eye disorders	accommodation disorder, mydriasis	acute glaucoma	blurred vision, dry eye

Ear and labyrinth disorders		tinnitus	
Cardiac disorders	palpitations, tachycardia, atrioventricular block, bundle branch block.	collapse conditions, worsening of cardiac failure, dysrhythmia, cardiomyopathies, torsades de pointes	hypersensitivity myocarditis, myocardial infarction, increased risk of sudden death has been suspected in cardiac patients
Vascular disorders	orthostatic hypotension	hypertension	hyperthermia, stroke, syncope

Respiratory, thoracic and mediastinal disorders	congested nose	allergic inflammation of the pulmonary alveoli and of the lung tissue, respectively (alveolitis, Löffler's syndrome)	
Gastrointestinal disorders	dry mouth, constipation, nausea	diarrhoea, vomiting, tongue oedema, salivary gland enlargement, paralytic ileus	epigastric distress, stomatitis, peculiar taste, black tongue
Hepatobiliary disorders		jaundice, hepatic impairment (e.g., cholestatic liver disease)	hepatitis
Skin and subcutaneous tissue disorders	hyperhidrosis	rash, urticaria, pruritis, face oedema, alopecia,	

		photosensitivity reaction	
Renal and urinary disorders	micturition disorders	urinary retention	urinary frequency, dilatation of urinary tract, syndrome of inappropriate ADH (antidiuretic hormone) secretion
Reproductive system and breast disorders	erectile dysfunction	galactorrhoea, gynaecomastia	breast enlargement, testicular swelling, libido fluctuations, interference with sexual function including impotence
General disorders and administration site conditions	fatigue, feeling thirst oedema, increased perspiration, hyperpyrexia	pyrexia	

Investigations	increased weight, nonspecific ECG changes and changes in AV conduction, abnormal electrocardiogram, prolonged QT electrocardiogram, prolonged QRS complex electrocardiogram, hyponatremia	increased intraocular pressure, decreased weight, abnormal liver function test, increased blood alkaline phosphatase, increased transaminases	

*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).

c. Description of selected adverse reactions

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.

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 including Monoamine Oxidase Inhibitors (MAOIs) and Selective Serotonin Reuptake Inhibitors (SSRIs) (see sections 4.3, 4.4 and 4.5).

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 during the first two weeks of dosage reduction. 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.

Side effects in enuresis

The doses 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. Infrequently, mild sweating and itching have been reported. Behavioural changes have been observed in children receiving tricyclics for treatment of enuresis.

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 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 to SAHPRA via the **"6.04 Adverse Drug Reaction Reporting Form",** found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

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.

Mixed poisoning with other central nervous system depressants is not uncommon.

Signs and symptoms

Overdosage and poisoning may be characterised by central nervous system depression or excitation, severe anticholinergic effects and cardiotoxicity.

The following symptoms and signs are characteristic of acute overdosage:

Anticholinergic symptoms

Mydriasis, tachycardia, urinary retention, dry mucous membranes, reduced bowel motility, temporary confusion, disturbed concentration, or transient visual hallucinations, vomiting, drowsiness, restlessness, ataxia, stupor and pyrexia. Convulsions and epileptiform seizures. Fever. Sudden occurrence of CNS depression. Lowered consciousness progressing into coma. Respiratory depression. Hyperreflexia may be present with extensor plantar reflexes. Hypothermia may occur.

Cardiac symptoms

Dysrhythmias (ventricular tachydysrhythmias, torsade de pointes, ventricular fibrillation) and other abnormalities such as bundle branch block, ECG evidence of impaired conduction, congestive heart failure.

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, hypokalaemia, hyponatraemia.

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 medicines or substances.

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.

Management

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 dysrhythmias
    - 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 medicines.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A.1.2 Psychoanaleptics (antidepressants)

Pharmacotherapeutic group: Antidepressants - Non-selective monoamine reuptake inhibitor (tricyclic antidepressant).

ATC Code: N 06 AA 09

Amitriptyline is a tricyclic antidepressant.

Amitriptyline causes inhibition of the membrane pump mechanism which is responsible for the reuptake of noradrenaline into adrenergic neurons. As the re-uptake of noradrenaline is

physiologically important in terminating the transmitting actions of noradrenaline, inhibition of the re-uptake may potentiate or prolong sympathetic activity. The antidepressant action of amitriptyline is believed to be due to this interference with re-uptake of noradrenaline. The precise mechanism of action in man has not yet been confirmed. Amitriptyline is not a monoamine oxidase inhibitor nor does it act primarily by stimulation of the central nervous system.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, amitriptyline is well absorbed from the gastrointestinal tract. Oral administration of tablets results in maximum serum levels in about 4 hours (t_{max} = 3,89 ± 1,87 hours; range 1,93 - 7,98 hours). After peroral administration of 50 mg the mean C_{max} = 30,95 ± 9,61 ng/mL; range 10,85-45,70 ng/mL (111,57 ± 34,64 nmol/L; range 39,06 - 164,52 nmol/L). The mean absolute oral bioavailability is 53 % (F_{abs} = 0,527 ± 0,123; range 0,219 - 0,756).

Distribution

Both amitriptyline and its primary active metabolite, nortriptyline are distributed throughout the body and are extensively bound to plasma and tissue protein. Plasma concentrations of both amitriptyline and nortriptyline differ widely between patients.

The apparent volume of distribution $(V_d)_\beta$ estimated after intravenous administration is 1221 L ± 280 L; range 769 - 1702 L (16 ± 3 L/kg).

The plasma protein binding is about 95 %.

Amitriptyline and the main metabolite nortriptyline pass across the placental barrier.

In nursing mothers, amitriptyline and nortriptyline are excreted in small amounts with the breast milk. The ratio milk concentration/plasma concentration in women is around 1:1. The estimated daily infant exposure (amitriptyline + nortriptyline) averages 2 % of the corresponding maternal weight related doses of amitriptyline (in mg/kg) (see section 4.6).

Biotransformation

Amitriptyline undergoes extensive liver metabolism.

In vitro the metabolism of amitriptyline proceeds mainly by demethylation (CYP2C19, CYP3A4) and hydroxylation (CYP2D6) followed by conjugation with glucuronic acid. Other isozymes involved are CYP1A2 and CYP2C9. The metabolism is subject to genetic polymorphism. The main active metabolite is the secondary amine, nortriptyline.

Nortriptyline is a more potent inhibitor of noradrenaline than of serotonin uptake, while amitriptyline inhibits the uptake of noradrenaline and serotonin equally well. Other metabolites such as cis- and trans-10 hydroxy amitriptyline and
cis- and trans 10 hydroxynortriptyline have the same profile as nortriptyline but is considerably weaker. Demethylnortriptyline and amitriptyline N oxide are only present in plasma in minute amounts; the latter is almost inactive. All the metabolites are less anticholinergic than amitriptyline and nortriptyline. In plasma the amount of total 10-hydroxynortriptyline dominates but most of the metabolites are conjugated.

Elimination

The elimination half-life ($t_{½}\,\beta$) of amitriptyline after peroral administration is about 25 hours (24,65 ± 6,31 hours) with an estimated range from about 16,49 - 40,36 hours which may be

considerably extended in overdosage. The mean systemic clearance (Cl_s) is 39,24 ± 10,18 L/h, range 24,53 - 53,73 L/h.

Excretion is via urine mainly as metabolites either in free or conjugated form. The renal elimination of unchanged amitriptyline is insignificant (about 2 %).

Steady state plasma levels of amitriptyline + nortriptyline are reached within a week for most patients, and in steady state the plasma level comprises approximately equal parts of amitriptyline and nortriptyline around the clock following treatment with conventional tablets 3 times a day.

Elderly patients

Longer half-lives and decreased oral (Cl_o) clearance values due to a reduced rate of metabolism have been demonstrated in elderly patients.

Reduced hepatic function

Hepatic impairment may reduce hepatic extraction resulting in higher plasma levels and caution should be exercised when dosing these patients.

Reduced renal function

Renal failure has no influence on the kinetics.

Polymorphism

The metabolism is subject to genetic polymorphism (CYP2D6 and CYP2C19).

Pharmacokinetic/pharmacodynamic relationship

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

The therapeutic plasma concentration in major depression is around 80 - 200 ng/mL (≈ 280 – 700 nmol/L) (for amitriptyline + nortriptyline). Levels above 300 - 400 ng/mL are associated with increased risk of disturbance in cardiac conduction in terms of prolonged QRS-complex or AV block.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate

Microcrystalline cellulose

Crospovidone

Maize starch

Anhydrous colloidal silica

Purified talc

Magnesium stearate

Film coating

Hypromellose

Purified talc

Titanium dioxide (E171)

Macrogol 6000

Brilliant blue FCF CI42090

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

HDPE bottle pack and PVC/aluminium blister pack

Store at or below 25 °C in well closed container (in the case of HDPE bottle pack).

Store in the original packaging until required for use.

Store in a cool dry place.

6.5 Nature and contents of container

Tablets are packed in

- HDPE bottles in pack sizes of 100, 500 or 1000 tablets.
- White opaque PVC/aluminium blister pack of 28, 30, 56, 60 and 100 tablets.

Not all pack sizes are marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

1 Sherborne Road

Parktown

JOHANNESBURG

2193

South Africa

Tel: 0860287835

8. REGISTRATION NUMBER

AMITRIPTYLINE 10 mg AUSTELL - 49/1.2/1017

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 November 2020

10. DATE OF REVISION OF THE TEXT

2023.07.26