SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

GULF AMITRIPTYLINE 25 film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

25 mg amitriptyline hydrochloride

Contains sugar; Lactose monohydrate 72,5 mg per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Yellow, round, biconvex, film-coated tablet plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

GULF AMITRIPTYLINE 25 is indicated in:

- The treatment of endogenous depression.
- Adjunctive therapy for nocturnal enuresis in children from 11 years of age where organic pathology has been excluded.

4.2 Posology and method of administration

Posology

Depression

Initial

One tablet (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 to 100 mg daily.

Treatment should be continued for at least three months before being gradually withdrawn.

Hospitalised patients may be given doses of up to 200 mg daily and, occasionally, up to 300 mg daily.

Dosage adjustment

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

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.

Nocturnal enuresis

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

Do not exceed the recommended dose.

GULF AMITRIPTYLINE 25 is not suitable for children under 11 years of age.

Duration of treatment

Treatment should not be continued for longer than 3 months.

Discontinuation

When stopping treatment for depression or nocturnal enuresis, GULF AMITRIPTYLINE 25 should be withdrawn gradually.

Special populations

Elderly patients and adolescents

In general, lower dosages are recommended for elderly patients and adolescents. 50 mg daily may be satisfactory in those adolescents and elderly patients who may not tolerate higher doses. The required daily dose may be administered either as divided doses or as a single dose preferably in the evening or at bedtime (see sections 4.4 and 5.2).

Renal impairment

GULF AMITRIPTYLINE 25 can be given in usual doses to patients with renal failure (see section 5.2).

Hepatic impairment

Use in patients with severe hepatic impairment is contraindicated (see section 4.3). Careful dosing and, if possible, a serum level determination is advisable in patients with hepatic impairment (see sections 4.4 and 5.2).

Cytochrome P450 inhibitors of CYP2D6

Depending on individual patient response, a lower dose of GULF AMITRIPTYLINE 25 should be considered if a strong CYP2D6 inhibitor (e.g. bupropion, quinidine, fluoxetine, paroxetine) is added to amitriptyline treatment (see section 4.5).
Amitriptyline serum levels may need to be monitored whenever GULF AMITRIPTYLINE 25 is to be co-administered with a strong CYP2D6 inhibitor (see section 4.5).

Known poor metabolisers of CYP2D6 or CYP2C19

These patients may have higher plasma concentrations of amitriptyline and its active metabolite nortriptyline. Consider a dose reduction of the recommended dose (see sections 4.5 and 5.2).

Method of administration

GULF AMITRIPTYLINE 25 is for oral use.
The tablets should be swallowed with water.

4.3 Contraindications

GULF AMITRIPTYLINE 25 is contraindicated in:

- Patients who have shown prior hypersensitivity to amitriptyline hydrochloride, tricyclic antidepressants or to any of the ingredients of GULF AMITRIPTYLINE 25 (see section 6.1)
- The acute phase after myocardial infarction and in patients with heart block (see section 4.4)
- History of myocardial infarction, dysrhythmias, congestive heart failure, coronary artery insufficiency (see section 4.4)
- The treatment of depression in children or adolescents below the age of 18 years (see sections 4.2 and 4.4)
- Patients receiving monoamine oxidase inhibitors (MAOIs) or for at least 14 days after their discontinuation (see sections 4.4 and 4.5) Concurrent use with linezolid (see section 4.5)
- Concurrent use with antihypertensive medicines (see section 4.5)

- Pregnancy and lactation (see section 4.6)
- Severe liver disease (see sections 4.2, 4.4 and 5.2)
- Mania (see section 4.4).

4.4 Special warnings and precautions for use

Tricyclic antidepressants such as GULF AMITRIPTYLINE 25 should at all times be kept out of reach of children, as even small doses may be fatal to them.

Anticholinergic effects

Peripheral anticholinergic side effects, notably dry mouth, constipation, urinary retention and pupillary dilatation with blurred vision and changes in visual accommodation may occur. When anticholinergic effects are severe, GULF AMITRIPTYLINE 25 should be discontinued or reduced.

Sedative effects

Drowsiness or excessive sedation may be caused in certain patients. At the time of initiation of therapy, drowsiness is often experienced, and 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 as drowsiness or excessive sedation may be caused in certain patients (see section 4.7). 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).

Elderly patients

Elderly patients are more prone to the anticholinergic and sedative effects, and therapy should be initiated at lower than standard doses in the elderly.
Elderly patients are particularly susceptible to orthostatic hypotension.
In elderly male patients suffering from prostatism, urinary retention may be precipitated.

Manic depressive psychosis

Caution should be exercised with patients suffering from a depressive phase of manic depressive psychosis, as occasionally hypomania or mania can be precipitated in such patients. Withdraw GULF AMITRIPTYLINE 25 if the depression turns into a manic phase (see section 4.3).

Cardiac disease

Cardiac dysrhythmias and severe hypotension are likely to occur with high dosage. They may also occur in patients with pre-existing heart disease taking normal dosage.

Due to the potential cardiotoxicity of GULF AMITRIPTYLINE 25, its use is contraindicated in the acute phase after myocardial infarction, in patients with heart block or with a history of myocardial infarction, dysrhythmias, congestive heart failure or coronary artery insufficiency (see section 4.3).
In patients suffering from cardiac disease, special caution should be observed because of the occasional problems of tachycardia, dysrhythmias, orthostatic hypotension and other unwanted effects on blood pressure, aggravation of conduction disturbances and electrocardiographic abnormalities. Regular cardiological and electrocardiographic examination is advised.

QT-interval prolongation and dysrhythmia can occur. Caution is advised in patients with significant bradycardia, in patients with uncompensated heart failure, or in patients concurrently taking QT-prolonging medicines.

Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) are known to be conditions increasing the prodysrhythmic risk.

Endocrine effects

Endocrine effects include changes in libido, interference with sexual function, gynaecomastia and breast enlargement, and galactorrhoea. Changes in blood sugar concentrations may also occur and, less frequently, inappropriate secretion of antidiuretic hormone.

Cautious use in certain conditions

Diabetes

Blood sugar concentrations may be altered in diabetic patients. As described for other psychotropics, GULF AMITRIPTYLINE 25 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.

Epilepsy

Epilepsy may be aggravated due to the epileptogenic potential of tricyclic antidepressants such as GULF AMITRIPTYLINE 25. Administer GULF AMITRIPTYLINE 25 with caution to patients with a history of epilepsy.

Glaucoma

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. Narrow-angle glaucoma may be aggravated.

Hepatic disease

Advanced hepatic disease may be aggravated by GULF AMITRIPTYLINE 25 and use of GULF AMITRIPTYLINE 25 in severe liver disease is contraindicated (see sections 4.2, 4.3 and 5.2).

Hyperthyroidism

Great care is necessary if GULF AMITRIPTYLINE 25 is administered to patients with hyperthyroidism or to those receiving thyroid medication, since cardiac dysrhythmias may develop (see section 4.5).

Paranoid symptomatology

Paranoid symptomatology may be aggravated by GULF AMITRIPTYLINE 25.

Phaeochromocytoma

GULF AMITRIPTYLINE 25 should be used with caution in patients with phaeochromocytoma.

Porphyria

The use of GULF AMITRIPTYLINE 25 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 GULF AMITRIPTYLINE 25 should be used with caution in these patients.

Prostatism

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

Urinary and gastrointestinal conditions

GULF AMITRIPTYLINE 25 should be used with caution in patients with urinary retention, pylorus stenosis, constipation or paralytic ileus as some of these conditions may be aggravated by GULF AMITRIPTYLINE 25.

Hyponatraemia

Hyponatraemia (usually in the elderly and possibly due to inappropriate secretion of antidiuretic hormone) has been associated with all types of antidepressants such as GULF AMITRIPTYLINE 25 and should be considered in all patients who develop drowsiness, confusion or convulsions while taking GULF AMITRIPTYLINE 25 (an antidepressant).

NOTE: Elderly patients are more prone to all these effects, and therapy should be initiated at lower than standard doses in the elderly (see section 4.2).

Skin conditions

GULF AMITRIPTYLINE 25 should be withdrawn if allergic skin reactions appear.

Co-administration of certain medicines

Anaesthetics

Anaesthetics given during tri/tetracyclic antidepressant therapy may increase the risk of dysrhythmias and hypotension. If possible, discontinue this GULF AMITRIPTYLINE 25 several days before surgery; if emergency surgery is unavoidable, the anaesthetist should be informed that the patient is being so treated (see section 4.3).

Anticholinergics

The simultaneous administration of anticholinergic medicines may be dangerous.

Central nervous system (CNS) depressants

GULF AMITRIPTYLINE 25 should not usually be given to patients receiving other central nervous system depressants, e.g. barbiturates, and to patients receiving monoamine oxidase inhibitors – only after a suitable interval has elapsed (the medicines may be given together if the dosages are carefully controlled, preferably in hospital) (see section 4.5).

Direct-acting sympathomimetics

The pressor effects of the direct-acting sympathomimetic medicines, adrenaline (epinephrine) and noradrenaline (norephinephrine), are enhanced. The hypotensive effect of certain antihypertensive medicines may be reduced (see section 4.5).

Selective Serotonin Reuptake Inhibitors (SSRIs)

GULF AMITRIPTYLINE 25 should be used with caution in patients receiving SSRIs (see sections 4.2 and 4.5).

Electroconvulsive therapy
Unless essential, it is inadvisable to combine GULF AMITRIPTYLINE 25 and electroconvulsive therapy (ECT).

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

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

Close supervision of patients and in particular those at high risk should accompany GULF AMITRIPTYLINE 25 therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Hyperpyrexia
Hyperpyrexia has been reported with tricyclic antidepressants, such as GULF AMITRIPTYLINE 25, when administered with anticholinergic or with neuroleptic medicines, especially in hot weather.

Serotonin syndrome
Concomitant administration of amitriptyline with buprenorphine may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5).

If concomitant treatment with buprenorphine is clinically warranted, careful observation of the patient is

advised, particularly during treatment initiation and dose increases.
Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms. If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

Severe cutaneous reactions (SCARs)
Severe cutaneous adverse reactions (SCARs) including drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported in association with amitriptyline, as in GULF AMITRIPTYLINE 25, treatment. Most of these reactions occurred within 2 to 6 weeks. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for cutaneous reactions.

If signs and symptoms suggestive of these reactions appear, GULF AMITRIPTYLINE 25 should be withdrawn immediately, treatment with GULF AMITRIPTYLINE 25 must not be restarted in this patient at any time and, an alternative treatment should be considered (as appropriate).

Withdrawal
After prolonged administration, abrupt cessation of therapy may produce withdrawal symptoms such as headache, malaise, insomnia and irritability. GULF AMITRIPTYLINE 25 should be withdrawn gradually to reduce the risk of withdrawal symptoms.

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.

Lactose warning
GULF AMITRIPTYLINE 25 contains 72,5 mg lactose monohydrate per tablet. Patients with the rare hereditary conditions of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take GULF AMITRIPTYLINE 25.

GULF AMITRIPTYLINE 25 may influence the glycaemic control of patients with diabetes mellitus (see section 4.4 – Diabetes).

Paediatric population

GULF AMITRIPTYLINE 25 is contraindicated in children or adolescents below the age of 18 years for the treatment of depression (see section 4.3). Long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are not available (see section 4.2).

4.5 Interaction with other medicines and other forms of interaction

Potential for amitriptyline to affect other medicines

Contraindicated combinations

Monoamine Oxidase Inhibitors (MAOIs)

MAOIs (non-selective as well as selective A (moclobemide) and B (selegiline)) – can potentiate the effects of tricyclic antidepressants such as GULF AMITRIPTYLINE 25 and hyperpyretic crises, severe convulsions, and fatalities have occurred. Also, an increased risk of developing “serotonin syndrome” (see sections 4.3 and 4.4).

Treatment with GULF AMITRIPTYLINE 25 should only commence after at least 14 days after the discontinuation of a monoamine oxidase inhibitor as severe hypertensive reactions and have been reported with concomitant use. Conversely, several days should elapse between withdrawing a tricyclic antidepressant such as GULF AMITRIPTYLINE 25 and starting a monoamine oxidase inhibitor.

Concomitant use of GULF AMITRIPTYLINE 25 and linezolid may result in CNS excitation and hypertension (see section 4.3).

Combinations that are not recommended

Adrenergic neurone blockers

Tricyclic antidepressants including GULF AMITRIPTYLINE 25 may counteract the antihypertensive effects of centrally acting antihypertensives such as reserpine, clonidine and methyldopa. It is advisable to review all antihypertensive therapy during treatment with GULF AMITRIPTYLINE 25. There is an increased risk of hypertension on clonidine withdrawal.

Alpha$_2$-adrenoceptor stimulants

Concomitant use of apraclonidine and brimonidine with GULF AMITRIPTYLINE 25 should be avoided.

Anticholinergic medicines

Tricyclic antidepressants, including GULF AMITRIPTYLINE 25 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, urinary retention or acute glaucoma (especially in elderly patients).

Antifungals

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

Buprenorphine

Concomitant use of buprenorphine with serotonergic medicines, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs), such as amitriptyline may increase the risk of serotonin syndrome, a potentially life-threatening condition (see section 4.4).

Disulfiram

Concomitant use of disulfiram may inhibit the metabolism of amitriptyline. Delirium has been reported in patients taking GULF AMITRIPTYLINE 25 with disulfiram.

Diuretics

Caution is also advised for co-administration of GULF AMITRIPTYLINE 25 and diuretics inducing hypokalaemia (e.g. furosemide) as there is an increased risk of postural hypotension.

Dopaminergics

Concomitant use of GULF AMITRIPTYLINE 25 and entacapone should be avoided. CNS toxicity has also been reported with selegiline.

Medicines which prolong the QT-interval

Antidysrhythmics such as quinidine, amiodarone, disopyramine, procainamide and propafenone, the antihistamines astemizole and terfenadine, some antipsychotics (notably pimozide and sertindole), cisapride, halofantrine, and sotalol may increase the likelihood of ventricular dysrhythmias when taken with tricyclic antidepressants including GULF AMITRIPTYLINE 25.

Methadone

Use caution when using GULF AMITRIPTYLINE 25 and methadone concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects.

Sibutramine

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

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).

Thioridazine

Co-administration of GULF AMITRIPTYLINE 25 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 GULF AMITRIPTYLINE 25 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.

Combinations requiring precautions for use

Anaesthetics

Concomitant therapy with GULF AMITRIPTYLINE 25 and anaesthetics may increase the risk of dysrhythmias and hypotension. If surgery is necessary, the anaesthetist should be informed that a patient is being treated with GULF AMITRIPTYLINE 25 (see section 4.4).

Antihypertensives

The antihypertensive effects of betanidine, debrisoquine, guanethidine and possibly of clonidine are reduced by tricyclic antidepressants.

CNS depressants

GULF AMITRIPTYLINE 25 may enhance the sedative effects of alcohol, barbiturates and other central

nervous system (CNS) depressants and anticonvulsants (i.e. carbamazepine) (see section 4.4).

Norepinephrine reuptake inhibitors (NRI)

Concomitant use of GULF AMITRIPTYLINE 25 and reboxetine should be used with caution.

Thyroid preparations

Patients taking thyroid preparations may show an accelerated response to GULF AMITRIPTYLINE 25. The use of GULF AMITRIPTYLINE 25 with thyroid hormones may precipitate cardiac dysrhythmias (see section 4.4).

Potential of other medicines to affect amitriptyline

Altretamine

Risk of severe postural hypotension.

Analgesics

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

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.

CYP inhibitors and inducers

General

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 (see sections 4.2 and 5.2).

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 and some SSRIs (e.g. fluoxetine, paroxetine, fluvoxamine). These medicines 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 strong inhibitor of CYP2D6. Dose adjustment of amitriptyline may be necessary (see section 4.2). Caution is advised in the case of co-administration of amitriptyline with duloxetine, a moderate CYP2D6 inhibitor.

CYP3A4 and CYP1A2 inhibitors
The CYP3A4 and CYP1A2 isozymes metabolise amitriptyline (as in GULF AMITRIPTYLINE 25) 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 GULF AMITRIPTYLINE 25 and strong CYP3A4 inhibitors such as ketoconazole, itraconazole and ritonavir. Ritonavir, a HIV-protease inhibitor, may increase the serum levels of amitriptyline. Therefore, careful monitoring of therapeutic and adverse effects is recommended when these medicines are administered concomitantly.

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. Serious adverse effects have been reported due to increased amitriptyline plasma concentration.

Cytochrome P450 inducers
Oral contraceptives, rifampicin, phenytoin, barbiturates, carbamazepine and St. John's Wort (*Hypericum perforatum*) may increase the metabolism of tricyclic antidepressants such as GULF AMITRIPTYLINE 25 and result in lowered plasma levels of tricyclic antidepressants and reduced antidepressant response.

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

Muscle relaxants
Concomitant use of baclofen enhances its muscle relaxant effect.

Nitrates

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

Estrogens and progestogens

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

Sodium valproate and valpromide

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

Tricyclic antidepressants and neuroleptics

Concomitant administration of tricyclic antidepressants, such as amitriptyline and neuroleptics (also known as antipsychotic medicines) may lead to a lowered convulsion threshold, and seizures due to the mutual inhibition of the metabolism of each other. It may be necessary to adjust the dosage of these medicines.

4.6 Fertility, pregnancy and lactation

Pregnancy

Use of GULF AMITRIPTYLINE 25 in pregnancy is contraindicated (see section 4.3).
Animal studies have shown reproductive toxicity.

Breastfeeding

GULF AMITRIPTYLINE 25 is contraindicated during breastfeeding (see section 4.3).
Amitriptyline and its metabolites are excreted into breast milk (corresponding to 0,6 % - 1 % of the maternal dose). A risk to the breastfed child cannot be excluded.

Fertility

No data on the effects of amitriptyline (as in GULF AMITRIPTYLINE 25) on human fertility are available. Amitriptyline reduced the pregnancy rate in rats.

4.7 Effects on ability to drive and use machines

GULF AMITRIPTYLINE 25 has a major influence on a patient’s ability to drive and use machines, especially at the time of initiation of therapy.
Adverse reactions such as drowsiness, dizziness and blurred vision have been reported in patients receiving amitriptyline as in GULF AMITRIPTYLINE 25.

At the time of initiation of therapy, patients should be advised not to drive a motor vehicle, climb dangerous heights, operate dangerous machinery or perform any tasks that require concentration, for at least several days until they are certain that GULF AMITRIPTYLINE 25 does not adversely affect their ability to do so (see section 4.8). In these situations, impaired decision making could lead to accidents. These adverse effects can be potentiated by the concomitant intake of alcohol and CNS depressant medicines (such as barbiturates) (see sections 4.4 and 4.5).

4.8 Undesirable effects

a. Summary of the safety profile

Amitriptyline, as in GULF AMITRIPTYLINE 25, may induce side effects similar to other tricyclic antidepressants. Frequent side effects may include aggression, confusion, drowsiness, excessive sedation, atrioventricular block, bundle branch block, orthostatic hypotension, dry mouth, urinary retention. Some of the 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. Severe cutaneous adverse reactions (SCARs), including drug reaction with eosinophilia and systemic symptoms (DRESS), have been reported in association with amitriptyline (see section 4.4).

b. Tabulated list of adverse reactions

System Organ Class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Less frequent	bone marrow depression including agranulocytosis, eosinophilia, leucopenia, thrombocytopenia, purpura
Immune system disorders	Less frequent	oedema of face and tongue, angioedema
	Frequency unknown	anaphylaxis
Endocrine disorders	Less frequent	syndrome of inappropriate ADH secretion (SIADH), hyperglycaemia, hypoglycaemia, hyponatraemia
Metabolism and nutrition disorders	Less frequent	decreased appetite, increased appetite, weight gain,

		weight loss, anorexia
	Frequency unknown	elevation or lowering of blood sugar levels
Psychiatric disorders	Frequent	aggression, confusional states, agitation
	Less frequent	hypomania or mania (see section 4.4), anxiety, insomnia, nightmares, delirium (in elderly patients), hallucinations, suicidal ideation or behaviour (see section 4.4), disorientation, excitement, restlessness, disturbed concentration, behavioural changes
	Frequency unknown	paranoia
Nervous system disorders	Frequent	somnolence, tremors, dizziness, headache, drowsiness or excessive sedation, speech disorders (dysarthria), disturbance in attention, dysgeusia, paraesthesia, ataxia
	Less frequent	convulsions, akathisia, polyneuropathy, peripheral neuropathy, numbness, incoordination,

		tremors, coma, epileptiform seizures, altered EEG, extrapyramidal disorder including abnormal involuntary movements and tardive dyskinesia
Eye disorders	Frequent	accommodation disorder, mydriasis, blurred vision
	Less frequent	acute glaucoma
	Frequency unknown	dry eye
Ear and labyrinth disorders	Less frequent	tinnitus
Cardiac disorders	Frequent	palpitations, tachycardia, atrioventricular block, bundle branch block
	Less frequent	myocardial infarction, heart block, dysrhythmias, non-specific ECG changes and changes in AV-conduction, cardiomyopathies, *torsades de pointes*
	Frequency unknown	hypersensitivity myocarditis, sudden death, worsening of cardiac failure
Vascular disorders	Frequent	orthostatic hypotension, hypotension
	Less frequent	hypertension, syncope, stroke
Respiratory, thoracic and mediastinal disorders	Frequent	congested nose
	Less frequent	allergic inflammation of the pulmonary alveoli and of the lung tissue, respectively (alveolitis,

		Löffler's syndrome)
Gastrointestinal disorders	Frequent	dry mouth, constipation, nausea, sour or metallic taste, gastric irritation
	Less frequent	diarrhoea, vomiting, tongue oedema, salivary gland enlargement, paralytic ileus, epigastric distress, dysgeusia, stomatitis, black tongue
Hepatobiliary disorders	Less frequent	jaundice, hepatic impairment (e.g. cholestatic liver disease), hepatitis
Skin and subcutaneous tissue disorders	Frequent	hyperhidrosis
	Less frequent	rash, urticaria, face oedema, alopecia, photosensitivity reaction
	Frequency unknown	pruritis, Drug reaction with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal and connective tissue disorders	Frequency unknown	increased risk of bone fractures (class effect)*
Renal and urinary disorders	Frequent	micturition disorders, urinary retention
	Less frequent	urinary tract dilation
Reproductive system	Frequent	erectile dysfunction,

and breast disorders		impotence, changes in libido, sexual dysfunction
	Less frequent	galactorrhoea, gynaecomastia, breast enlargement, testicular swelling
General disorders and administrative site conditions	Frequent	fatigue, feeling thirsty, hyperthermia
	Less frequent	pyrexia, weakness
Investigations	Frequent	abnormal electrocardiogram, electrocardiogram QT prolonged, electrocardiogram QRS complex prolonged, hyponatremia
	Less frequent	liver function test abnormal, increased blood alkaline phosphatase, increased transaminases

*See below section c for description of selected adverse reactions.

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.

Withdrawal symptoms

The symptoms associated with withdrawal of tricyclic antidepressants such as GULF AMITRIPTYLINE 25, particularly after prolonged administration, include gastrointestinal disturbances such as nausea; generalised somatic symptoms such as malaise, chills, headache, itching and increased perspiration; irritability, restlessness, anxiety and agitation; sleep disturbances (insomnia and vivid dreams); parkinsonism or akathisia; hypomania or mania (reported rarely, occurring within 2 - 7 days of stopping chronic therapy with tricyclic antidepressants); cardiac dysrhythmias. These symptoms are not indicative of addiction. Withdrawal symptoms seem to be more

common and more severe in children.

Adverse reactions such as withdrawal symptoms, respiratory depression and agitation have been reported in neonates whose mothers had taken tricyclic antidepressants in the last trimester of pregnancy.

Side-effects in enuresis

As dosages used in enuresis are low compared to those used for depression, side-effects are less frequent. The most common 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.

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 Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Alternately you can contact Gulf Drug Company (Pty) Ltd at +27 31 538 8700 or per info@gulfdrug.co.za.

4.9 Overdose

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.
Overdose with GULF AMITRIPTYLINE 25 in children could have serious consequences. Children are especially susceptible to coma, cardiotoxicity, respiratory depression, seizures and hyponatraemia, lethargy, sinus tachycardia, drowsiness, nausea, vomiting and hyperglycaemia. During awakening possibly again confusion, agitation and hallucinations and ataxia.

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: drowsiness, restlessness, ataxia, stupor, coma, pyrexia, palpitations, tachycardia,

cardiac dysrhythmias and hypotension. Epileptiform seizures may occur. Marked antimuscarinic effects may occur, including dryness of the mouth, dilated pupils, tachycardia, urinary retention and intestinal stasis.

Severe symptoms include unconsciousness, convulsions and myoclonus, hyperreflexia, hypotension and respiratory and cardiac depression, with life-threatening cardiac dysrhythmias that may recur some days after apparent recovery.
Mixed poisoning with other central nervous system depressants is not uncommon.

Cardiac symptoms
Dysrhythmias (ventricular tachydysrhythmias, 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, hypokalaemia, hyponatraemia may occur.

Management of overdose
Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 1.2 Psychoanaleptics (antidepressants)
Pharmacotherapeutic group: Antidepressants - Non-selective monoamine reuptake inhibitor (tricyclic antidepressant)
ATC code: N 06 AA 09

Mechanism of action
Amitriptyline is a tricyclic antidepressant. It has marked anticholinergic and sedative properties. It prevents the re-uptake, and hence the inactivation of noradrenaline (norepinephrine) and serotonin at nerve terminals. Reuptake prevention of these monoamine neurotransmitters potentiates their action in the brain. This is associated with the antidepressant activity.

5.2 Pharmacokinetic properties

Absorption

Oral administration of the tablets results in a maximum serum level in about 4 hours (t_{max}=3,89 ± 1,87 hours; range 1,93 - 7,98 hours). After per oral 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).
After oral administration amitriptyline is absorbed slowly but completely. Due to the often delayed gastrointestinal tract passage maximum plasma concentrations are reached after 1 to 5 (-8) hours.

Distribution

The apparent volume of distribution (Vd)β 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

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 (see sections 4.2 and 4.4). The main active metabolite is the secondary amine, nortriptyline.

Nortriptyline is a more potent inhibitor of noradrenaline (norephinephrine) than of serotonin uptake, while amitriptyline inhibits the uptake of noradrenaline (norephinephrine) and serotonin equally well. Other metabolites such as cis- and trans-10-hydroxyamitriptyline 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 ($t_{1/2}$ β amitriptyline after peroral administration is about 25 hours (24,65 ± 6,31 hours; range 16,49 - 40,36 hours). The mean systemic clearance (Cls) is 39,24 ± 10,18 L/h, range 24,53 - 53,73 L/h.
The excretion proceeds mainly with urine. 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.

Pharmacokinetics in special patient groups

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 (see section 4.2).

Reduced renal function

Renal failure has no influence on the kinetics.

Polymorphism

The metabolism is subject to genetic polymorphism (CYP2D6 and CYP2C19) (see section 4.2).

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

Colloidal silicon dioxide

Lactose monohydrate

Magnesium stearate

Maize starch

Purified talc

Film-coating

Opadry II Yellow (85F32568)

Purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

PVC/Al blister strips and HDPE containers: 48 months.

White PP containers: 24 months.

Patient ready packs (LDPE): 24 months.

6.4 Special precautions for storage

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

Keep HDPE/PP containers and/or patient ready packs (PRPs) tightly closed.

Do not remove tablets from containers/blister strips/PRPs until required for use.

6.5 Nature and contents of container

Unit carton containing 28, 56 or 84 tablets in clear PVC/silver printed Aluminium blister strips of 14 or 28 tablets each.

White HDPE containers of 100, 500 or 1000 tablets.

White PP containers of 84, 100 or 500 tablets.

Printed LDPE patient ready packs containing 28, 56 or 84 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Gulf Drug Company (Pty) Ltd
22 Burnside Drive
Old Mill Industrial Park
Mount Edgecombe
4300
Tel: +27 31 538 8700

8. REGISTRATION NUMBER

A40/1.2/0605

9. DATE OF FIRST AUTHORISATION

19 March 2010.

10. DATE OF REVISION OF THE TEXT

10 June 2026.