CLEAN PROPOSED PROFESSIONAL INFORMATION FOR AMDERIP

SCHEDULING STATUS

S5

1 NAME OF THE MEDICINE

AMDERIP 10 (film-coated tablets)

AMDERIP 25 (film-coated tablets)

AMDERIP 50 (film-coated tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

AMDERIP 10

Each film-coated tablet contains 10 mg amitriptyline hydrochloride

Contains sugar: lactose monohydrate 10 mg.

AMDERIP 25

Each film-coated tablet contains 25 mg amitriptyline hydrochloride

Contains sugar: lactose monohydrate 10 mg.

AMDERIP 50

Each film-coated tablet contains 50 mg amitriptyline hydrochloride

Contains sugar: lactose monohydrate 20 mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

AMDERIP 10

Round blue colored biconvex tablets debossed 1 on one side and plain on other side.

AMDERIP 25

Round yellow colored biconvex tablets plain on both sides.

AMDERIP 50

Round brown colored biconvex tablets plain on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

AMDERIP is indicated for the treatment of depression in adults (18 years and older).

4.2 Posology and method of administration

Posology

Adults:

Initially 75 mg to 150 mg daily in divided doses.

Maintenance dose is 50 mg to 100 mg daily in divided doses.

Method of administration

Amitriptyline is for oral use.

The tablets should be swallowed with water.

4.3 Contraindications

AMDERIP is contraindicated in:

- Patients with hypersensitivity to amitriptyline or to any of the excipients (see section 6.1).
- Concurrent use with monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping treatment with MAOIs (see section 4.5).
- Concurrent use with linezolid.
- Concurrent use with antihypertensive medicines (see section 4.5).
- Recent myocardial infarction, dysrhythmias, particularly heart block to any degree, congestive heart failure, coronary artery insufficiency.
- Pregnancy and lactation (see section 4.6).

- Children under 18 years of age.
- Mania.
- Severe liver disease.

4.4 Special warnings and precautions for use

AMDERIP should at all times be kept out of reach of children as even small doses may be fatal to them.

Anticholinergic effects

Peripheral anticholinergic adverse events such as dry mouth, constipation and urinary retention may occur. Patients may also experience pupillary dilatation, blurred vision and changes in visual accommodation. When anticholinergic affects are severe, **AMDERIP** should be discontinued or the dosage should be reduced.

Sedative effects

Drowsiness, excessive sedation, disorientation and agitation may be caused in certain patients. Insomnia and restlessness may also occur. Drowsiness is often experienced at the start of treatment with **AMDERIP**.

Cardiac disease

Special caution should be observed in patients suffering from cardiac disease, as tachycardia, cardiac dysrhythmias, orthostatic hypotension and other unwanted effects on blood pressure may occur. There may also be an increase in conduction disturbances and electrocardiographic abnormalities. Regular cardiological and electrocardiographic examination is advised.

Elderly patients are particularly susceptible to orthostatic hypotension.

There is an increased risk of ventricular dysrhythmias when **AMDERIP** is used with medicines which prolong the QT interval.

Endocrine effects

Endocrine effects include changes in libido, sexual dysfunction, gynaecomastia, breast

enlargement and galactorrhoea.

Changes in blood sugar concentrations may also occur and less frequently, hyponatraemia which may be due to the inappropriate secretion of antidiuretic hormone (ADH).

Manic depressive psychosis

Caution should be observed with patients suffering from manic depressive psychosis as a shift towards the manic phase may occur. Should the patient enter into a manic phase, amitriptyline should be discontinued.

Suicidal tendencies

Patients with a history of suicide-related events or those experiencing a significant degree of suicidal ideation prior to the start of treatment should receive careful monitoring during treatment, as they are known to be at greater risk of suicidal thoughts or attempts.

Direct acting sympathomimetic and anaesthetics

The pressor effects of the direct-acting sympathomimetic medicines, epinephrine (adrenaline) and norepinephrine (noradrenaline) are potentiated by **AMDERIP**.

Anaesthetics containing these vasoconstrictors should be avoided as hypertensive reactions may occur. When possible, treatment should be discontinued several days before elective surgery. If emergency surgery is unavoidable, the anaesthetist should be informed that the patient is being treated with **AMDERIP**.

Tricyclic antidepressants may counteract the antihypertensive effects of centrally acting antihypertensives.

Porphyria

AMDERIP should be used with caution in patients suffering from acute forms of porphyria.

Cautious use in certain conditions

AMDERIP should be used with caution in patients with a history of epilepsy, impaired liver function, cardiovascular disease, urinary retention, prostatic hypertrophy, hyperthyroidism, constipation, paralytic ileus and narrow angled glaucoma as these conditions may be aggravated by amitriptyline.

Skin conditions

AMDERIP should be withdrawn if allergic skin reactions appear.

Co-administration of certain medicines

AMDERIP may enhance the effects of central nervous system depressants such as alcohol, and barbiturates and anticholinergic medicines. Concomitant use should be avoided.

Electroconvulsive therapy

Unless essential, it is not advisable combine **AMDERIP** and electroconvulsive therapy (ECT).

Hyponatraemia

Hyponatraemia may be due to inappropriate excretion of the antidiuretic hormone

Elderly patients are particularly susceptible to these adverse events and treatment should be initiated at lower than standard doses.

Lactose warning

AMDERIP contains lactose which may have an effect on the glycaemic control in patients with diabetes mellitus. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

After prolonged administration, abrupt cessation of treatment may produce withdrawal symptoms namely headache, malaise, insomnia or irritability.

4.5 Interaction with other medicines and other forms of interaction

Simultaneous administration of monoamine oxidase inhibitors (MAOIs) and **AMDERIP** may cause serotonin syndrome (a combination of symptoms such as hyperthermia, convulsions, myoclonus, confusion, agitation). A minimum of 14 days should elapse between discontinuation of a MAOI and starting **AMDERIP**, which should be introduced cautiously and dosage increased gradually (see section 4.3).

AMDERIP may counteract the antihypertensive effects of debrisoquine, bethanidine and clonidine (see section 4.3).

There is an increased risk of hypertension on clonidine withdrawal. All antihypertensive therapy should be reviewed during treatment with **AMDERIP**.

Antibacterials: Concomitant use of **AMDERIP** and linezolid may result [~~l~~]in CNS excitation and hypertension (see section 4.3). Plasma concentrations of amitriptyline may be reduced by rifampicin which reduces the antidepressant effect.

Concomitant use **AMDERIP** and reboxetine should be used with caution.

The plasma concentrations of amitriptyline, found in **AMDERIP**, may be increased by selective serotonin reuptake inhibitors (SSRIs). Fluoxetine which is an SSRI, significantly inhibits cytochrome P450 II D6, which is involved in the metabolism of **AMDERIP** and therefore significantly decreases the metabolism of **AMDERIP** which results in increased plasma concentrations. Patients should be monitored for increased antidepressant plasma levels and toxicity when **AMDERIP** is used concurrently with fluoxetine. Dosage adjustments of **AMDERIP** and/or fluoxetine may be required.

Alpha$_2$-adrenocepter stimulants: Concomitant used of apraclonidine and brimonidine with **AMDERIP** should be avoided.

Analgesics: The risk of central nervous system (CNS) toxicity with **AMDERIP** is increased with tramadol. There is a possibility of increased sedation with opioid analgesics.

Anaesthetics: Concomitant therapy with **AMDERIP** and anaesthetics may increase the risk of dysrhythmias and hypotension. If surgery is necessary, the anaesthetist should be informed that the patient is being treated with **AMDERIP.**

Antidysrhythmics: Medicines which prolong the QT interval such as amiodarone, disopyramide, procainamide, propafenone and quinidine may increase the likelihood of ventricular dysrhythmias when taken with tricyclic antidepressants. Concomitant use with **AMDERIP** should be avoided.

AMDERIP should not be given with sympathomimetic medicines such as epinephrine (adrenaline), isoprenaline, norepinephrine (noradrenaline), phenylephrine, and phenylpropanolamine due to hypertension and dysrhythmias.

Methylphenidate may inhibit the metabolism of amitriptyline contained in **AMDERIP** and therefore increase the antidepressant effect of **AMDERIP**.

AMDERIP may enhance the response to alcohol, barbiturates and other CNS depressants.

Concomitant use of disulfiram may inhibit the metabolism of amitriptyline.

Concomitant use of **AMDERIP** and antiepileptics may lead to a lower convulsive threshold and seizures. Dosage adjustments may be necessary.

Barbiturates and carbamazepine may reduce the antidepressant effect of **AMDERIP**.

Antifungals: Fluconazole may increase serum concentrations of amitriptyline found in **AMDERIP**.

Antihistamines: Increased sedative and anticholinergic effects may occur when antihistamines are used concurrently with **AMDERIP**.

Antivirals: The protease inhibiter, ritonavir, may increase the serum levels of amitriptyline, found in **AMDERIP**, whose metabolism is mediated through cytochrome P450 isoenzymes. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are used concomitantly.

Antipsychotics: Concomitant use of amitriptyline, which is found in **AMDERIP**, with pimozide and thioridazine may lead to an increased risk of ventricular dysrhythmias. Avoid concomitant use with pimozide and thioridazine. Concomitant use with antipsychotics may increase the plasma levels of amitriptyline and increase the anticholinergic effects of phenothiazines and possibly clozapine.

Beta-blockers: There is an increased risk of ventricular dysrhythmias when **AMDERIP** is taken with sotalol.

Calcium channel blockers: Verapamil and diltiazem may increase plasma concentrations of amitriptyline found in **AMDERIP**.

Diuretics: There is an increased risk of postural hypotension.

Dopaminergics: Concomitant use of **AMDERIP** and entacapone should be avoided. CNS toxicity has been reported with selegiline.

Muscle relaxants: Concomitant use of baclofen enhances the muscle relaxant effect.

Nitrates: Reduced effect of sublingual nitrates (due to dry mouth).

Estrogens and progestogens: Oral contraceptives antagonise the antidepressant effect of **AMDERIP** but adverse effects may be increased due to increased plasma concentrations of

tricyclic antidepressants as per **AMDERIP**.

Excessive anticholinergic effects may occur when **AMDERIP** is combined with anticholinergic medicines. Paralytic ileus, urinary retention or acute glaucoma may be precipitated in elderly patients.

Cimetidine may reduce the hepatic metabolism of **AMDERIP** which may lead to increased plasma levels of amitriptyline.

St. John's Wort may reduce plasma concentrations of amitriptyline which is found in **AMDERIP** thus decreasing the antidepressant effect.

Patients taking thyroid preparations may show an accelerated response to **AMDERIP.** Concomitant use of **AMDERIP** with thyroid hormones may precipitate cardiac dysrhythmias.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety and efficacy of **AMDERIP** during pregnancy has not been established (see section 4.3).

Only limited data are available regarding exposed pregnancies. Animal studies have shown reproductive toxicity.

Breastfeeding

Safety and efficacy of **AMDERIP** during lactation has not been established (see section 4.3).

Mothers on **AMDERIP** should not breastfeed their babies (see section 4.3).

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

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.

Since adverse reactions such as drowsiness, dizziness and blurred vision have been reported

in patients receiving **AMDERIP**, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that **AMDERIP** does not adversely affect their ability to do so (see section 4.8).

4.8 Undesirable effects

a. Summary of the safety profile

AMDERIP may induce adverse events similar to other tricyclic antidepressants. Some of the below mentioned adverse events 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.

b. Tabulated summary of adverse reactions

MedDRA system organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Less frequent	Bone marrow depression including agranulocytosis, eosinophilia, leucopoenia, thrombocytopenia and purpura
Immune system disorders	Less frequent	Hypersensitivity reactions including skin rash, urticaria, photosensitization, oedema of face and tongue, angioedema
Endocrine disorders	Less frequent	Syndrome of inappropriate ADH secretion (SIADH), hyperglycaemia, hypoglycaemia, hyponatraemia
Metabolism and nutrition disorders	Less frequent	Increased appetite, weight gain, weight loss, anorexia
Psychiatric disorders	Less frequent	Confusional state, disorientation, agitation, insomnia, nightmares, delusions,

MedDRA system organ class	**Frequency**	**Adverse reactions**
		hallucinations, mania or hypomania, excitement, anxiety, restlessness, disturbed concentration, behavioural changes, suicidal thoughts or behaviour
Nervous system disorders	Frequent	Drowsiness or excessive sedation
	Less frequent	Dizziness, headache, peripheral neuropathy, numbness, paraesthesia, ataxia, tremors, coma, convulsions, altered EEG, extrapyramidal disorder including dysarthria (speech disorder), tardive dyskinesia and abnormal involuntary movements
Eye disorders	Frequent	Accommodation disorder, blurred vision, increased intra-ocular pressure
	Less frequent	Mydriasis
Ear and labyrinth disorders	Less frequent	Tinnitus
Cardiac disorders	Less frequent	Tachycardia, palpitations, myocardial infarction, heart block, dysrhythmias, changes in atrioventricular conduction, nonspecific ECG changes
Vascular disorders	Less frequent	Hypotension, hypertension, postural hypotension, syncope, stroke
Gastrointestinal disorders	Frequent	Dry mouth, constipation
	Less frequent	Diarrhoea, vomiting, nausea, paralytic ileus,

MedDRA system organ class	**Frequency**	**Adverse reactions**
		epigastric distress, dysgeusia, metallic taste, stomatitis, parotid swelling, black tongue
Hepato-biliary disorders	Less frequent	Hepatitis (including hepatic impairment and cholestatic jaundice)
Skin and subcutaneous tissue disorders	Less frequent	Rash, alopecia
Musculoskeletal and connective tissue disorders	Less frequent	Increased risk of bone fractures
Renal and urinary disorders	Frequent	Urinary retention
	Less frequent	Urinary frequency, urinary tract dilation
Reproductive system and breast disorders	Less frequent	Gynaecomastia, breast enlargement, galactorrhoea, testicular swelling, changes in libido, impotence, sexual dysfunction
General disorders and administration site conditions	Frequent	Hyperthermia
	Less frequent	Fatigue, weakness, increased perspiration

AMDERIP should be used with caution in patients with a history of epilepsy, impaired liver function, urinary retention, prostatic hypertrophy, hyperthyroidism and narrow angled glaucoma as these conditions may be aggravated by **AMDERIP**.

Peripheral anticholinergic adverse events notably dry mouth, constipation, urinary retention and pupillary dilatation with blurred vision and changes in visual accommodation, have been reported. When anticholinergic affects are severe, **AMDERIP** should be discontinued or reduced.

Simultaneous administration of monoamine oxidase inhibitors (MAOIs) and **AMDERIP** may cause serotonin syndrome (a combination of symptoms such as hyperthermia, convulsions, myoclonus, confusion, agitation). A minimum of 14 days should elapse between discontinuation of a MAOI and starting **AMDERIP**, which should be introduced cautiously and dosage increased gradually (see section 4.3).

Caution should be observed with patients suffering from manic depressive psychosis as a shift towards the manic phase may occur. Should the patient enter into a manic phase, amitriptyline should be discontinued.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Overdosage and poisoning may be characterised by central nervous system depression or excitation, severe anticholinergic effects and cardiotoxicity. The signs and symptoms of an overdosage include: drowsiness, restlessness, ataxia, coma, stupor, cardiac dysrhythmias, pyrexia, palpitations, hypotension, tachycardia, convulsions and respiratory depression. Mixed poisoning with other central nervous system depressants is not uncommon.

Treatment for overdosage 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: N06AA09

Amitriptyline is a tricyclic antidepressant. It has marked anticholinergic and sedative properties. It prevents the re-uptake, and hence the inactivation of noradrenaline and serotonin at nerve terminals. Re-uptake prevention of these monoamine neurotransmitters potentiate their action in the brain. This appears to be associated with the antidepressant activity.

5.2 Pharmacokinetic properties

Absorption

Amitriptyline is absorbed after oral administration, reaching its maximum plasma concentration approximately 6 hours after administration.

Distribution

Amitriptyline and nortriptyline are widely distributed throughout the body with a high binding to plasma proteins and tissues. An elimination half-life ranging from 9 - 25 hours has been estimated.

Amitriptyline and nortriptyline pass across the placental barrier. In nursing mothers, amitriptyline and nortriptyline, are excreted in the breast milk.

Biotransformation

Amitriptyline is extensively demethylated in the liver to its primary active metabolite, nortriptyline. The metabolism pathway includes N-oxidation and conjugation with glucuronic acid.

Elimination

Amitriptyline is excreted as glucuronide or conjugate sulfate metabolites and little medicine appears unchanged in the urine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Colloidal silicon dioxide

Corn maize starch

Croscarmellose sodium

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Talc

Tablet coating AMDERIP 10:

Hypromellose

Macrogol 6000

Macrogol (E1521)

Polyvinyl alcohol (E1203)

Talc (E553b)

Titanium dioxide (E171)

FD&C Blue #1/Brilliant Blue FCF Aluminum Lake (E133)

Tablet coating AMDERIP 25:

Hypromellose

Iron oxide yellow (E172)

Macrogol 6000

Macrogol (E1521)

Polyvinyl alcohol (E1203)

Talc (E553b)

Titanium dioxide (E171)

Tablet coating AMDERIP 50:

Hypromellose

Iron oxide yellow (E172)

Iron oxide red (E172)

Macrogol 6000

Macrogol (E1521)

Polyvinyl alcohol (E1203)

Talc (E553b)

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years. Store at or below 25 °C.

6.4 Special precautions for storage

No special precautions for storage exist for **AMDERIP**.

6.5 Nature and contents of container

AMDERIP 10 are packed in PVC/PVdC/Aluminium blisters containing 30 film-coated tablets. The blister strips are packed in a printed carton.

AMDERIP 25 are packed in PVC/PVdC/Aluminium blisters containing 30 or 60 film-coated tablets. The blister strips are packed in a printed carton.

AMDERIP 50 are packed in PVC/PVdC/Aluminium blisters containing 30 film-coated tablets.

The blister strips are packed in a printed carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Strides Pharma SA (Pty) Ltd

106 16th Road

Building 2

Midrand

8 REGISTRATION NUMBER(S)

AMDERIP 10: 54/1.2/0684.681

AMDERIP 25: 54/1.2/0685.682

AMDERIP 50: 54/1.2/0686.683

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29 March 2022

10 DATE OF REVISION OF THE TEXT