1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS S5

PROPRIETARY NAME AND DOSAGE FORM

TREPILINE 10 (tablets)

TREPILINE 25 (tablets)

COMPOSITION

TREPILINE 10: Each tablet contains 10 mg amitriptyline hydrochloride.

Excipients:

Colloidal silicon dioxide, disodium edetate, indigo carmine aluminium lake 73015, lactose monohydrate, macrogol, magnesium stearate, polyvinyl alcohol, starch (maize), starch (pregelatinised), sunset yellow FCF aluminium lake 15985, talc, titanium dioxide 77891, quinolene yellow aluminium lake 47005.

Contains sugar: Lactose monohydrate 60 mg.

TREPILINE 25: Each tablet contains 25 mg amitriptyline hydrochloride.

Excipients:

Colloidal silicon dioxide, disodium edetate, indigo carmine aluminium lake 73015, iron oxide yellow 77492, lactose monohydrate, macrogol, magnesium stearate, polyvinyl alcohol, starch (maize), starch (pregelatinised), sunset yellow FCF aluminium lake 15985, talc, titanium dioxide 77891, quinolene yellow aluminium lake 47005.

Contains sugar: Lactose monohydrate 40 mg.

CATEGORY AND CLASS

A 1.2 Psychoanaleptics (antidepressants)

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Amitriptyline is a tricyclic antidepressant that inhibits the membrane pump mechanism responsible for re-uptake of noradrenaline into adrenergic neurons. This interference with re-uptake of noradrenaline is believed to result in the antidepressant activity of amitriptyline. The precise mechanism of action in man has not been confirmed.

Pharmacokinetic properties

Absorption

After oral intake, peak plasma concentrations occur within about 6 hours of oral administration.

Distribution

Amitriptyline and nortriptyline are widely distributed throughout the body and are highly bound to plasma and tissue protein. The estimated half-life of amitriptyline is 9 to 25 hours. It crosses the placental barrier and is excreted in breast milk.

Metabolism

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

It is excreted in urine in the form of metabolites.

INDICATIONS

TREPILINE is a tricyclic antidepressant indicated in the treatment of patients 18 years and older with depression.

CONTRAINDICATIONS

TREPILINE is contraindicated in:

- Patients with hypersensitivity to amitriptyline or to any of the excipients (see COMPOSITION).
- Myocardial infarction.
- History of myocardial infarction, dysrhythmias, particularly heart block to any degree, congestive heart failure, coronary artery insufficiency.
- Concurrent use with monoamine oxidase inhibitors or within 14 days of stopping treatment with MAOIs (see INTERACTIONS).
- Concurrent use with linezolid.
- Concurrent use with antihypertensive medicines (see INTERACTIONS).
- Pregnancy and lactation (see HUMAN REPRODUCTION).
- Children under 18 years of age.
- Mania.
- Severe liver disease.

WARNINGS AND SPECIAL PRECAUTIONS

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

Drowsiness is often experienced at the start of TREPILINE therapy.

Anticholinergic effects

Peripheral anticholinergic side effects, notably dry mouth, constipation, urinary retention and pupillary dilatation with blurred vision and changes in visual accommodation have been reported. When anticholinergic effects are severe, TREPILINE should be discontinued or reduced.

Sedative effects

Drowsiness or excessive sedation may be caused in certain patients and disorientation and agitation, insomnia and restlessness may occur.

Cardiac disease

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.

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.

Manic depressive psychosis

Caution should be observed with patients suffering from a depressive phase of manic depressive psychosis, as occasionally mania can be precipitated in such patients. TREPILINE should be withdrawn if the depression develops into a manic phase.

Suicidal tendencies

Patients with suicidal tendencies should be carefully supervised during treatment. Cases of suicidal ideation and suicidal behaviours have been reported during TREPILINE therapy or early after treatment discontinuation.

Direct-acting sympathomimetics and anaesthetics

The pressor effects of the direct-acting sympathomimetic agents, epinephrine and norepinephrine, are enhanced by TREPILINE, and local anaesthetics containing these vasoconstrictors should be avoided as hypertensive reactions may occur. When possible, treatment should be discontinued several days before elective surgery. The hypotensive effect of certain antihypertensive agents may be reduced.

Porphyria

The use of TREPILINE 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 TREPILINE should be used with caution in these patients.

Cautious use in certain conditions

TREPILINE should also be used with caution in patients with hyperthyroidism or with impaired liver function, and in those with a history of epilepsy, untreated narrow-angle glaucoma, urinary retention, prostatic hypertrophy or constipation. These conditions may be aggravated by TREPILINE.

Skin conditions

TREPILINE should be withdrawn if allergic skin reactions appear.

Co-administration of certain medicines

Effects of central nervous system depressants (including barbiturates and alcohol) and anticholinergic agents may be increased by TREPILINE. Co-administration should be avoided.

Electroconvulsive therapy

Unless essential, it is inadvisable to combine TREPILINE and electroconvulsive therapy (ECT).

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 TREPILINE and should be considered in all patients who develop drowsiness, confusion or convulsions while taking TREPILINE (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.

Lactose warning

TREPILINE contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus. TREPILINE contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take TREPILINE.

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 TREPILINE, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that TREPILINE does not adversely affect their ability to do so (see SIDE EFFECTS).

INTERACTIONS

Monoamine oxidase inhibitors (MAOIs) can potentiate the effects of tricyclic antidepressants such as TREPILINE and hyperpyretic crises, severe convulsions, and fatalities have occurred. A minimum of 14 days should elapse between discontinuing a MAOI and starting TREPILINE, which should be introduced cautiously and dosage increased gradually (see CONTRAINDICATIONS).

TREPILINE may block the antihypertensive action of debrisoquine, bethanidine and clonidine (see CONTRAINDICATIONS). There is an increased risk of hypertension on clonidine withdrawal. All antihypertensive therapy should be reviewed during treatment with TREPILINE.

Concomitant use of TREPILINE and reboxetine should be used with caution.

The plasma concentrations of amitriptyline in TREPILINE may be increased by selective serotonin reuptake inhibitors (SSRIs). Fluoxetine markedly inhibits cytochrome P450 II D6, which is involved in the metabolism of a number of tricyclic antidepressants such as TREPILINE. Patients should be monitored for increased antidepressant plasma levels and toxicity when fluoxetine is used concurrently with TREPILINE. Adjustment of the dosage of TREPILINE and/or fluoxetine may be necessary.

Alpha$_2$-adrenoceptor stimulants: Concomitant use of apraclonidine and brimonidine with TREPILINE should be avoided.

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

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

Antidysrhythmics: There is an increased risk of ventricular dysrhythmias when TREPILINE is used with medicines which prolong the QT interval, including amiodarone, disopyramide, procainamide, propafenone and quinidine. Concomitant use is to be avoided.

Antibacterials: Plasma concentrations of amitriptyline in TREPILINE may be reduced by rifampicin which reduces the antidepressant effect. Concomitant use of TREPILINE and linezolid may result in CNS excitation and hypertension (see CONTRAINDICATIONS).

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

Methylphenidate may inhibit the metabolism of amitriptyline, as contained in TREPILINE, and therefore increase the antidepressant action of TREPILINE.

TREPILINE may enhance the response to alcohol, barbiturates and other CNS depressants. Concomitant use of disulfiram may inhibit the metabolism of amitriptyline. Delirium has been reported in patients taking TREPILINE with disulfiram.

Concomitant use of TREPILINE and antiepileptics may lower the convulsive threshold.

Barbiturates and carbamazepine may decrease the antidepressant action of TREPILINE.

Antifungals: Increased serum concentrations of amitriptyline, as contained in TREPILINE, have occurred in patients also taking fluconazole. Serious adverse effects have been reported due to increased amitriptyline plasma concentration.

Antihistamines: Increased anticholinergic and sedative effects may occur when antihistamines are used with TREPILINE.

Based on the known metabolism of amitriptyline, as contained in TREPILINE, the protease inhibitor, ritonavir, may increase the serum levels of amitriptyline, as contained in TREPILINE. Therefore, careful monitoring of therapeutic and adverse effects is recommended when these medicines are administered concomitantly.

Antipsychotics: Increased risk of ventricular dysrhythmias. Avoid concomitant use with pimozide or thioridazine. Concomitant use with antipsychotics may increase plasma concentrations of amitriptyline, as contained in TREPILINE, and increase the anticholinergic side effects of phenothiazines and possibly clozapine.

Beta-blockers: There is an increased risk of ventricular dysrhythmias associated with concomitant use of TREPILINE and sotalol.

Calcium-channel blockers: Diltiazem and verapamil may increase the plasma concentration of amitriptyline.

Diuretics: There is an increased risk of postural hypotension.

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

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

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

Oestrogens and progestogens: Oral contraceptives antagonise the antidepressant effect of TREPILINE but side effects may be increased due to increased plasma concentrations of tricyclic antidepressants such as TREPILINE.

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

Cimetidine is reported to reduce hepatic metabolism of TREPILINE. Concomitant use enhances the sedative effect.

St. John's Wort may decrease plasma levels of amitriptyline.

TREPILINE may increase levels of thioridazine leading to cardiac side effects.

Patients taking thyroid preparations may show an accelerated response to TREPILINE. The use of TREPILINE with thyroid hormones may precipitate cardiac dysrhythmias.

HUMAN REPRODUCTION

Safety and efficacy during pregnancy and lactation have not been established (see CONTRAINDICATIONS).

Lactation

Mothers on TREPILINE should not breastfeed their babies.

DOSAGE AND DIRECTIONS FOR USE

Adults:

Initially 75 mg to 150 mg daily in divided doses.

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

SIDE EFFECTS

Blood and the lymphatic system disorders

Less frequent: Bone marrow depression including agranulocytosis, eosinophilia, leucopaenia, thrombocytopaenia and purpura

Immune system disorders

Less frequent: Hypersensitivity reactions including skin rash, urticaria, photosensitisation, 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 states, disorientation, agitation, insomnia, nightmares, delusions, hallucinations, mania or hypomania, excitement, anxiety, restlessness, disturbed concentration, behavioural changes, suicidal ideation, suicidal behaviour

Nervous system disorders

Frequent: Drowsiness or excessive sedation

Less frequent: Dizziness, headache, peripheral neuropathy, numbness, tingling and paraesthesia of the extremities, incoordination, ataxia, tremors, coma, epileptiform seizures, altered EEG, extra-pyramidal symptoms including abnormal involuntary movements and tardive dyskinesia, dysarthria

Eye disorders

Frequent: Blurred vision, accommodation disturbance, increased intra-ocular pressure

Less frequent: Mydriasis

Ear and labyrinth disorders

Less frequent: Tinnitus

Cardiac disorders

Less frequent: Palpitations, tachycardia, myocardial infarction, heart block, non-specific ECG changes and changes in AV-conduction, dysrhythmias

Vascular disorders

Less frequent: Hypotension, syncope, postural hypotension, hypertension, stroke

Gastrointestinal disorders

Frequent: Dry mouth, constipation

Less frequent: Nausea, vomiting, diarrhoea, paralytic ileus, epigastric distress, dysgeusia, stomatitis, metallic taste, parotid swelling, black tongue

Hepato-biliary disorders

Less frequent: Hepatitis (including altered liver function and cholestatic jaundice)

Skin and subcutaneous tissue disorders

Less frequent: Skin rash, alopecia

Musculoskeletal, connective tissue and bone disorders

Frequency unknown: Increased risk of bone fractures (class effect)

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 administrative site conditions

Frequent: Hyperthermia

Less frequent: Weakness, fatigue, increased sweating

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

See SIDE EFFECTS.

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, hypotension, and in severe cases, respiratory depression. Epileptiform seizures may occur. Mixed poisoning with other central nervous system depressants is not uncommon.

Treatment

Treatment is symptomatic and supportive.

IDENTIFICATION

TREPILINE 10: Pale blue, round, shallow, biconvex, film-coated tablets, plain on both sides.

TREPILINE 25: Yellow, round, shallow, biconvex, film-coated tablet, plain on both sides.

PRESENTATION

TREPILINE 10:

Packs of 100 and 500 tablets in white polypropylene securitainers together with a foam insert/rayon and professional information which is sealed with white, low density polyethylene securitainer caps.

Packs of 28 tablets into metallised patient ready packs which are sealed with lay-flat zips after filling and packed into polyethylene bags.

TREPILINE 25: Packs of 100 and 500 tablets in white polypropylene securitainers together with a foam insert / rayon and professional information which is sealed with white low density polyethylene securitainer caps.

Packs of 28 and 84 tablets into metallised patient ready packs which are sealed with lay-flat zips after filling and packed into polyethylene bags.

Not all packs and pack sizes are necessarily marketed.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

Protect from light and moisture.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

TREPILINE 10: J/1.2/219

TREPILINE 25: J/1.2/220

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION FOR HUMAN USE

Date of registration: 11 October 1976

Date of the most recently revised professional information as approved by Council: 28 July 2017

Namibia:
Trepiline 10: NS3 90/1.2/001241
Trepiline 25: NS3 90/1.2/001242

Botswana:
Trepiline 10: NS3 B9322960 S2
Trepiline 25: NS3 BOT0801152 S2

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