1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S5

PROPRIETARY NAME

Noriline 10 mg tablets

Noriline 25 mg tablets

COMPOSITION

Per tablet:

Amitriptyline hydrochloride	10 mg
Amitriptyline hydrochloride	25 mg

PHARMACOLOGICAL CLASSIFICATION

A 1.2 Psychoanaleptics (antidepressants)

PHARMACOLOGICAL ACTION

Noriline (Amitriptyline hydrochloride) is a tricyclic antidepressant which potentiates the actions of biogenic amines in the central nervous system by preventing the re-uptake of noradrenaline and serotonin at nerve terminals. This leads to its antidepressant and sedative activity. It exhibits anti-cholinergic properties in the autonomic nervous system.

INDICATIONS

- Treatment of endogenous depression.

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

CONTRAINDICATIONS

Amitriptyline hydrochloride should be avoided in:

- patients who have known sensitivity to amitriptyline
- the immediate recovery phase after myocardial infarction and in patients with heart block
- not recommended for treatment of depression in children
- patients receiving monoamine oxidase inhibitors or for at least 14 days after their discontinuation
- safety in pregnancy and lactation has not been established.

WARNINGS

At the time of initiation of therapy, patients should be advised not to drive a motor vehicle, climb dangerous heights or operate dangerous machinery. In these situations, impaired decision making could lead to accidents. Psychosis may be activated in schizophrenic patients and manic-depressive patients may switch to a manic phase; use is not recommended in mania.

DOSAGE AND DIRECTIONS FOR USE

<u>Depression</u>:

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Treatment should be continued for at least three months before being gradually withdrawn. 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 to 20 mg at bedtime

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

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

SIDE EFFECTS AND SPECIAL PRECAUTIONS

Side effects:

Anti-cholinergic:

- The antimuscarinic action of Noriline causes a dry mouth, sour or metallic taste, constipation which may lead to paralytic ileus, urinary retention, blurred vision and disturbances in accommodation, palpitations, tachycardia, and impotence.

Central nervous system and neuromuscular:

- Drowsiness (but sometimes nervousness and insomnia may occur), headache, peripheral neuropathy, tremor, orthostatic hypotension, less frequently hypertension, dizziness, sweating, weakness and fatigue, ataxia, epileptiform seizures, extrapyramidal symptoms including speech difficulties, tinnitus, stomatitis and gastric irritation with nausea and vomiting. Confusion and delirium may occur, particularly in the elderly.

Allergic:

- Allergic skin rash, urticaria, photosensitisation, oedema of face and tongue.

Haematologic:

- Cholestatic jaundice and blood disorders, including eosinophilic, bone marrow depression, thrombocytopenia, leucopenia, and agranulocytosis.

Cardiovascular:

- Tricyclic antidepressants have an adverse effect on the myocardium and can cause conduction defects and cardiac arrhythmia; an increased risk of sudden death has been suspected in cardiac patients receiving tricyclic antidepressants. Hypotension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block and strokes can occur.

Endocrine:

- Changes in libido, interference with sexual function, gynaecomastia and breast enlargement, and galactorrhoea.

Other:

- Changes in blood sugar concentrations can also occur, and less frequently inappropriate secretion of antidiuretic hormone.
- Anorexia with mass loss, or mass gain, sometimes with abnormal appetite (carbohydrate craving) may occur.

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, symptoms including irritability, restlessness and dream and sleep disturbances. These are not indicative of addiction. Instances of mania or hypomania occurring within two to seven days following cessation of prolonged therapy with tricyclic antidepressants have been reported. Sweating and itching have been reported.

Special precautions:

- Noriline should be used with caution in patients with cardiovascular disease, hyperthyroidism or with impaired liver function, and in those with a history of epilepsy, untreated narrow-angle glaucoma, urinary retention, prostatic hypertrophy, or constipation. Patients with suicidal tendencies should be carefully supervised during treatment.
- Blood sugar concentrations can be altered in diabetic patients.
- Elderly patients adolescents and children can be especially sensitive to the side-effects of tricyclic antidepressants; reduced dosage should be used.
- Drowsiness is often experienced at the start of tricyclic antidepressant therapy and patients, if affected, should not drive or operate machinery.

Drug interactions:

- Noriline should not be given to patients receiving monoamine oxidase inhibitors for at least 14 days after their discontinuation; severe hypertensive reactions have been reported. Several days should elapse between withdrawing a tricyclic antidepressant and starting a monoamine oxidase inhibitor.
- Local anaesthetics containing direct-acting sympathomimetic agents, adrenaline and noradrenaline, must be used with great caution because of enhanced adrenergic effects when used together with Noriline.
- The metabolism of Noriline is increased by barbiturates and other enzyme inducers such as anti-epileptics while neuroleptics, cimetidine, methylphenidate, and possibly oestrogens and oral contraceptives reduce it.
- Noriline increases the effects of the central nervous system depressants including alcohol and anti-muscarinic agents.
- Hyperthyroid patients or those taking thyroid preparations can show an enhanced response to tricyclic antidepressants.

- The effects of bethanidine, debrisoquine, guanethidine and possibly of clonidine are reduced by tricyclic antidepressants.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Symptoms of overdosage are excitement and restlessness with marked antimuscarinic effects, 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 arrhythmias that may recur some days after apparent recovery.

Treatment is symptomatic and supportive.

IDENTIFICATION

10 mg:	A pale blue, biconvex, film-coated tablet, scored on one side, with a white to off-white core
25 mg:	A pale yellow, biconvex, film-coated tablet, scored on one side, with a white to off-white core

PRESENTATION

Tablets 10 mg:	100 in securitainers
	500 in securitainers
Tablets 25 mg:	100 in securitainers
	500 in securitainers
	28 and 84 in polypropylene vials

STORAGE INSTRUCTIONS

Store below 25 °C in well closed containers.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

Tablets 10 mg: Y/1.2/270

Tablets 25 mg: Y/1.2/271

NAME AND BUSINESS ADDRESS OF THE APPLICANT

Pharmacare Limited

Healthcare Park

Woodlands Drive

Woodmead 2191

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