Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Prothiaden 25 mg Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 25 mg dosulepin hydrochloride.

Excipients with known effect:
Lactose monohydrate 106 mg per hard capsule; soya lecithin.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard.

A red/brown hard gelatin capsule containing a white to off-white powder. The identifying code "P25" is printed on the capsule.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Prothiaden is indicated for the management of depression and associated anxiety.

4.2 Posology and method of administration

For oral administration.

Adults: The usual total daily dose is 75 mg to 150 mg in divided doses or as a single night-time dose. Treatment should be initiated at the lower dose. In certain circumstances, *e.g.* in hospital use, dosages up to 225 mg daily have been used.

Suggested regimens: 25 or 50mg three times daily or, alternatively, 75 or 150 mg as a single dose at night. Should the regimen of 150 mg as a single night-time dose be adopted, it is better to give a smaller dose for the first few days.

Elderly: 50 to 75 mg daily initially. As with any antidepressant, the initial dose should be increased with caution under close supervision. Half the normal adult dose may be sufficient to produce a satisfactory clinical response.

Children: Not recommended.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Contains soya lecithin. If you are allergic to peanut or soya, do not use this medicinal product.

Prothiaden is contra-indicated following recent myocardial infarction, and in patients with any degree of heart block or other cardiac arrhythmias. It is also contra-indicated in mania, severe liver disease, narrow angle glaucoma or other causes of increased intraocular pressure.

4.4 Special warnings and precautions for use

It may be two to four weeks from the start of treatment before there is an improvement in the patient's depression; the subject should be monitored closely during this period. The anxiolytic effect may be observed within a few days of commencing treatment.

The elderly are particularly liable to adverse effects with tricyclic antidepressants, especially agitation, confusion and postural hypotension.

Similarly to other tricyclic antidepressants, it has anticholinergic, antihistaminic and anti-a1 adrenergic effects which may cause common adverse effects. For a better control of these adverse effects, it is recommended to start with a low dose and increasing gradually until a therapeutic dose is achieved.

Prothiaden should be avoided in patients with a history of epilepsy and in patients with urinary retention. Use with caution in patients with cardiovascular disorders.

Tricyclic antidepressants potentiate the central nervous depressant action of alcohol. Anaesthetics given during tricyclic antidepressant therapy may increase the risk of arrhythmias and hypotension. If surgery is necessary, the anaesthetist should be informed that a patient is being so treated (see section 4.5).
On stopping treatment, it is recommended that antidepressants should be withdrawn gradually, wherever possible. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Suicide/suicidal thoughts or clinical worsening
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 drugs 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 drug 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.

Use in children and adolescents under 18 years of age
Prothiaden should not be used in the treatment of depression in children and adolescents under the age of 18 years. Studies in depression in this age group did not show a beneficial effect for tricyclic antidepressants. Studies with other classes of antidepressants have shown risk of suicidality, self-harm and hostility to be related to these compounds. This risk cannot be excluded with prothiaden. In addition, prothiaden is associated with a risk of cardiovascular adverse events in all age groups. Furthermore, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are not available (see also section 4.8 Undesirable effects and Section 4.9 Overdose).

4.5 Interaction with other medicinal products and other forms of interactions

Prothiaden should not be given concurrently with a monoamine oxidase inhibitor, nor within fourteen days of ceasing such treatment. The concomitant administration of Prothiaden and SSRIs should be avoided since increases in plasma tricyclic antidepressant levels have been reported following the co-administration of some SSRIs.

Prothiaden may alter the pharmacological effect of some concurrently administered drugs including CNS depressants such as alcohol and narcotic analgesics; the effect of these will be potentiated as will be the effects of adrenaline and noradrenaline

(some local anaesthetics contain these sympathomimetics). Anaesthetics given during tricyclic antidepressant therapy may increase the risk of arrhythmias and hypotension.

Prothiaden has quinidine like actions on the heart. For this reason, the use of drugs that affect cardiac conduction or prolong the QT interval may increase the risk of arrhythmias when taken with tricyclic antidepressants.

The use of tricyclics with thyroid hormones may precipitate cardiac arrhythmias.

In general, the hypotensive effect of antihypertensives is enhanced by tricyclic antidepressants, but there may be antagonism of the effect of adrenergic neurone blockers and of clonidine. It is advisable to review all antihypertensive therapy during treatment with tricyclic antidepressants.

4.6 Fertility, pregnancy and lactation

Treatment with Prothiaden should be avoided during pregnancy unless there are compelling reasons. There is inadequate evidence of the safety of the drug during human pregnancy.

There is evidence that dosulepin is secreted in breast milk but this is at levels which are unlikely to cause problems.

4.7 Effects on ability to drive and use machines

Initially, Prothiaden may impair alertness. Patients likely to drive or operate machinery should be warned of this possibility.

4.8 Undesirable effects

The following adverse effects, although not necessarily all reported with dosulepin, have occurred with other tricyclic antidepressants:

Atripine-like side effects including dry mouth, disturbance of accommodation, constipation, hesitancy of micturition and sedation are common early in treatment, but usually lessen.

Dizziness is also a common side effect of tricyclic antidepressants.

Uncommon adverse effects include drowsiness, sweating, postural hypotension, tremor skin rashes, tachycardia, confusion and hallucinations. Interference with sexual function may occur.

Potentially serious adverse effects are rare. These include depression of the bone marrow, agranulocytosis, hepatitis (including altered liver function), cholestatic jaundice, convulsions and inappropriate ADH secretion.

Psychotic manifestations, including mania and paranoid delusions, may be exacerbated during treatment with tricyclic antidepressants.

Cases of suicidal ideation and suicidal behaviours have been reported during dosulepin therapy or early after treatment discontinuation (see section 4.4).

Withdrawal symptoms may occur on abrupt cessation of tricyclic therapy and include insomnia, irritability and excessive perspiration. Similar symptoms in neonates whose mothers received tricyclic antidepressants during the third trimester have also been reported.

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

<u>Class effects</u>
Epidemiological studies, mainly 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 the risk is unknown.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected

adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms of overdosage may include dryness of the mouth, excitement, ataxia, drowsiness, loss of consciousness, muscle twitching, convulsions, widely dilated pupils, hyperreflexia, sinus tachycardia, cardiac arrhythmias, hypotension, hypothermia, depression of respiration, visual hallucinations, delirium, urinary retention, paralytic ileus, and respiratory or metabolic alkalosis.

Treatment should consist of gastric lavage. When the patient is unconscious or the cough reflex depressed, the lungs should be protected by a cuffed endotracheal tube. Repeated gastric/intestinal aspiration or repeated administration of activated charcoal may remove the drug and metabolites excreted into the gut via the bile. Continuous ECG monitoring is advisable. Abnormalities of cardiac rhythm and epileptic convulsions may occur and should be treated accordingly. Forced diuresis is not recommended. Bedrest is advisable, even after recovery.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Dosulepin is a tricyclic antidepressant which acts by inhibiting the re-uptake of monoamine neurotransmitters into presynaptic neurone at central nervous system, so producing a clinical antidepressant effect.

Dosulepin, in common with other tricyclics, inhibits the reuptake of noradrenaline and 5-hydroxytryptamine, with a significantly greater action on the uptake of noradrenaline. In addition, dosulepin inhibits the neuronal uptake of dopamine.

As a consequence of its effects on monoamine levels, dosulepin appears to produce adaptive changes in the brain

Similarly to other tricyclic antidepressants, it has anticholinergic, antihistaminic and anti-α1 adrenergic effects.

5.2 Pharmacokinetic properties

Dosulepin is readily absorbed from the gastrointestinal tract and extensively metabolised in the liver. Metabolites include northiaden, dosulepin-S-oxide and northiaden-S-oxide. Dosulepin is excreted in the urine, mainly in the form of metabolites; appreciable amounts are also excreted in the faeces. A half-life of about 50 hours has been reported for dosulepin and its metabolites.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsules Contents
Lactose monohydrate
Maize starch
Magnesium stearate

Capsule shell

Capsule cap
Red iron oxide (E 172)
Yellow iron oxide (E 172)
Erythrosine (E127)
Titanium dioxide (E 171)
Gelatin

Capsule body
Red iron oxide (E 172)
Titanium dioxide (E 171)
Gelatin

Printing ink
Opacode S-I-7305 HV white containing:
Titanium dioxide (E 171)
Shellac
Soya lecithin
Dimeticone

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25ºC. Keep the container tightly closed in order to protect from moisture. Store in the original package in order to protect from light.

6.5 Nature and contents of container

An amber-coloured glass bottle containing 100, 500 or capsules
Or
A high density polyethylene bottle with a cap and aluminium-faced pulpboard liner. The caps for packs which contain 100 units or less will be clic-loc cap, for those containing more than 100 units per pack; the cap will be a standard polypropylene cap.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements

7 MARKETING AUTHORISATION HOLDER

Teofarma S.R.L.
Valle Salimbene (PV)
Via F. LLI Cervi
8 CAP 27010
Italy

8 MARKETING AUTHORISATION NUMBER

PA1235/005/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 12 January 2007

10 DATE OF REVISION OF THE TEXT

August 20202