SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Prothiaden Capsules 25 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Prothiaden Capsule contains 25 mg Dosulepin Hydrochloride BP.

3. PHARMACEUTICAL FORM

Red/brown, hard gelatin capsules bearing the overprint 'P25' in white.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Prothiaden is indicated in the treatment of symptoms of depressive illness, especially where an anti-anxiety effect is required.

Due to its toxicity in overdose, Dosulepin should only be used in patients intolerant of or unresponsive to alternative treatment options (see section 4.4 and 4.9).

Initiation of treatment for patients who have not previously received Dosulepin should be restricted to specialist care prescribers.

4.2. Posology and method of administration

For oral administration

Adults: Initially 75 mg/day in divided doses or as a single dose at night, increasing to 150 mg/day. In certain circumstances, *e.g.* in hospital use, dosages up to 225 mg daily have been used.

Suggested regimens: 25 or 50 mg 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

Prothiaden is contraindicated following recent myocardial infarction, and in patients with any degree of heart block or other cardiac arrhythmias. It is also contraindicated in mania and severe liver disease and in patients with known hypersensitivity to Dosulepin or any of the ingredients.

4.4. Special warnings and precautions for use

Toxicity in overdose
Dosulepin is associated with high mortality in overdose. There is a low margin of safety between the (maximum) therapeutic dose and potentially fatal doses. Onset of toxicity occurs within 4-6 hours.

- A limited number of tablets should be prescribed to reduce the risk from overdose for all patients and especially for patients at risk of suicide.
- A maximum prescription equivalent to two weeks supply of 75mg/day should be considered in patients with increased risk factors for suicide at initiation of treatment, during any dosage adjustment and until improvement occurs.
- Avoid concomitant medications which may increase the risk of toxicity associated with dosulepin (See Section 4.5). Patients should be advised to store the tablets securely, out of sight and reach of children.
- In cases of overdoses, patients should seek IMMEDIATE MEDICAL ATTENTION (see section 4.9).

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 experience adverse effects with antidepressants, especially agitation, confusion and postural hypotension.

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.

Prothiaden should be avoided in patients with a history of epilepsy, thyroid disease, mania or urinary retention and in those with narrow-angle glaucoma or symptoms suggestive of prostatic hypertrophy. Patients with hepatic impairment and those undergoing electroconvulsive therapy should also avoid Prothiaden use.

Dosulepin may increase the risk of cardiovascular toxicity (cardiac arrhythmias, conduction disorders, cardiac failure and circulatory collapse), especially in the elderly. Caution should be exercised in using Dosulepin in the elderly and in patients with suspected cardiovascular disease (see Section 4.3).

Tricyclic antidepressants potentiate the central nervous depressant action of alcohol. Anaesthetics given during tri/tetracyclic 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.

On stopping treatment, it is recommended that antidepressants should be withdrawn gradually, wherever possible.

4.5. Interaction with other medicinal products and other forms of interaction

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 tri/tetracyclic antidepressant therapy may increase the risk of arrhythmias and hypotension.

Prothiaden has quinidine-like actions on the heart. For this reason, its concomitant use with other drugs which may affect cardiac conduction (*e.g.* sotalol, terfenadine, astemizole, halofantrine) should be avoided.

The hypotensive activity of certain antihypertensive agents (*e.g.* bethanidine, debrisoquine, guanethidine) may be reduced by Prothiaden. It is advisable to review all antihypertensive therapy during treatment with tricyclic antidepressants.

There is an increased risk of postural hypotension when tricyclic antidepressants are given with diuretics.

Tricyclic antidepressants may also antagonise the anticonvulsant effect of antiepileptics (convulsive threshold decreased).

Barbiturates may decrease and methylphenidate may increase the serum concentration of dosulepin and thus affect its antidepressant action.

There is no evidence that dosulepin interferes with standard laboratory tests.

4.6. Pregnancy and lactation

Treatment with Prothiaden should be avoided during pregnancy, unless there are compelling reasons. The safety of the drug during pregnancy has not been adequately studied.

There is evidence that dosulepin is secreted in breast milk. Although this is at levels which are unlikely to cause problems, caution should be exercised when prescribing to breastfeeding women.

4.7. Effects on ability to drive and use machines

Initially, Prothiaden may impair alertness; patients likely to drive vehicles 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:

Atropine-like side effects including dry mouth, disturbances of accommodation, tachycardia, constipation and hesitancy of micturition are common early in treatment, but usually lessen.

Other adverse effects include drowsiness, sweating, postural hypotension, tremor, increased intraocular pressure, hyponatremia, hypersensitivity reactions, skin rashes, changes in blood sugar levels, endocrine side effects and movement disorders. Interference with sexual function may also 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.

Class effects
Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRs and TCAs. The mechanism leading to this 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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

4.9. Overdose

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

Patients ingesting >5 mg/kg should seek immediate medical attention.

All children ingesting dosulepin should be assessed by a physician.

Onset of toxicity occurs within 4-6 hours after tricyclic antidepressant overdose.

Management
- A clear airway and adequate ventilation should be ensured. Hypoxia and acid-base imbalances should be corrected by assisted ventilation and iv sodium bicarbonate as appropriate.
- Do not give flumazenil to reverse benzodiazepine toxicity in mixed overdoses.
- The use of activated charcoal should be considered as a preferred initial means of reducing absorption in patients presenting within 2 hours of ingestion.
- The benefit of gastric lavage is uncertain and the technique should be avoided in any patients with an impaired airway.
- Blood pressure, pulse and cardiac rhythm should be monitored for at least 6 hours after ingestion.
- Arrhythmias are best treated by correcting hypoxia and acid-base disturbances. Specialist poisons advice should be sought before using any antiarrhythmic agents as these may exacerbate the arrhythmia.

- In cases of cardiac arrest, persist with prolonged CPR (for at least 1hr).
- Convulsions should be controlled with iv diazepam or lorazepam.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Dosulepin is a tricyclic antidepressant which acts by increasing transmitter levels at central synapses, 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 reuptake 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 by reducing or down-regulating both noradrenaline receptor numbers and noradrenaline-induced cyclic-AMP formation.

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

Maize starch, magnesium stearate, lactose, gelatin, red iron oxide, yellow iron oxide, yellow iron oxide, erythrocin, titanium dioxide, shellac, polymethylsiloxane, soya lecithin.

6.2. Incompatibilities

None stated.

6.3. Shelf life

Unopened shelf-life is 36 months for all pack size.

6.4. Special precautions for storage

None stated.

6.5. Nature and contents of container

A 28 pack child resistance blister with cover foil: 20 μm hard temper aluminium foil and deep-drawing foil: transparent PVC foil, hard. Thickness: 250μm. 2 blisters per pack, each containing 14 capsules.

6.6. Special precautions for disposal

None stated.

7. MARKETING AUTHORISATION HOLDER

Teofarma S.r.l.
Via F.lli Cervi, 8
27010 Valle Salimbene (PV)
Italy

8. MARKETING AUTHORISATION NUMBER(S)

PL 16250/0005

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

23/07/2007

10. DATE OF REVISION OF THE TEXT

13/03/2017