SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Thaden Tablets 75mg
Dosulepin Tablets 75mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 75mg dosulepin hydrochloride

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Coated tablet for oral administration
A round, red film coated, biconvex tablet embossed “PTN 75”

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dosulepin hydrochloride 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

Adults: Initially 75mg/day in divided doses or as a single dose at night, increasing to 150mg/day. In certain circumstances, e.g. in hospital use, dosages up to 225mg daily have been used. Suggested regimes: 25 or 50mg three times a day or alternatively, 75 or 150mg as a single dose at night. Should the regimes of 150mg as a single dose be adopted, it is better to give a smaller dose for the first few days.

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

Children: Not recommended

4.3 Contraindications

- Recent myocardial infarction.
- Any degree of heart block or other cardiac arrhythmias.
- Mania.
- Severe liver disease.
- Hypersensitivity to dosulepin or to any of the excipients.

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 overdose, patients should seek IMMEDIATE MEDICAL ATTENTION (see section 4.9)

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.

Dosulepin should be avoided in epileptic patients.

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 is using dosulepin in the elderly and in patients with suspected cardiovascular disease (see section 4.3).

Administration should be avoided if possible in patients with narrow angle glaucoma and symptoms suggestive of prostatic hypertrophy.

Care should be exercised if a patient receiving treatment undergoes surgery as anaesthetics may increase the risk of arrhythmias and hypotension. If surgery is required the anaesthetist should be informed that the patient is being so treated.

Care should be taken where there is a history of mania or psychoses. Dosulepin may aggravate psychotic symptoms. Patients posing a high suicidal risk require close supervision.

Conduction defects or cardiac arrhythmias may occur in hyperthyroid patients.

Toxic levels of dosulepin may develop in patients with severe renal disease.

The elderly are especially liable to experience adverse reactions to antidepressants, especially agitation, confusion and postural hypotension.

After initiating antidepressant therapy, it may be two to four weeks before there is an improvement in the patient's depression.~~;~~ It is important that the patient is carefully monitored during this period. The anxiolytic effect may be observed within a few days of commencing treatment.

It is recommended that antidepressants should be withdrawn gradually, as withdrawal reactions may occur.

Patients posing a high suicidal risk require close supervision.
Dosulepin hydrochloride should be given with caution to patients with a history of mania, history of urinary retention, or in patients with hepatic impairment, phaeochromocytoma, porphyria, and used with caution in patients having concurrent electroconvulsive therapy.

Blood sugar concentrations may be altered and as such dosulepin should be used in caution in diabetic patients.

Tricyclic antidepressants potentiate the central nervous depressant action of alcohol.

Hyponatraemia (usually in the elderly and possibly due to inappropriate secretion of antidiuretic hormone) has been associated with all types of antidepressants and should be considered in all patients who develop drowsiness, confusion or convulsions while taking an antidepressant.

Contains E124; which may cause allergic reactions in some people.

Contains lactose; patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Dosulepin hydrochloride should not be given concurrently with an MAO inhibitor nor within fourteen days of ceasing such treatment.

Dosulepin hydrochloride may alter the pharmacological effect of some concurrently administered drugs including CNS depressants such as alcohol and narcotic analgesics; the effects of these will be potentiated as will be the effects of adrenaline and noradrenaline (some local anaesthetics contain these sympathomimetics).

Concurrent administration with SSRIs should be avoided since increases in plasma tricyclic antidepressant levels have been reported following the co administration of some SSRIs.

Drugs which prolong the QT interval including antiarrhythmics such as quinidine, the antihistamines astemizole and terfenadine, some antipsychotics (notably pimozide and sertindole), cisapride, halofantrine and sotalol may increase the likelihood of ventricular arrhythmias when taken with tricyclic antidepressants and concurrent use should be avoided.

The problem may be exacerbated where the interacting drug (such as quinidine or some antipsychotics) also reduces tricyclic metabolism.

Antimuscarinic side effects may be enhanced by concurrent use with antimuscarinic drugs.

Antidepressants may antagonise the activity of antiepileptics by lowering the convulsive threshold.

Oral contraceptives may antagonise the antidepressant effect but side effects may be increased due to increased plasma concentrations of tricyclics.

There is an increased risk of postural hypotension on concurrent use with diuretics. The hypotensive activity of certain antihypertensive agents (eg betanidin debrisoquine, guanethidine) may be reduced by dosulepin hydrochloride. It would be advisable to review all antihypertensive therapy during treatment with tricyclic antidepressants.

Anaesthetics given during tricyclic antidepressant therapy may increase the risk of arrhythmias and hypotension. If surgery is necessary, the anaesthetist should be informed that the patient is being so treated.

Barbiturates and other enzyme inducers such as rifampicin and some antiepileptics may increase the metabolism of tricyclic antidepressants and result in lowered plasma concentrations and reduced antidepressant response.

Cimetidine, methylphenidate, antipsychotics and calcium channel blockers (eg diltiazem, verapamil) may reduce the metabolism and increase plasma levels of tricyclics.

4.6 Pregnancy and lactation

Treatment with dosulepin hydrochloride should be avoided during pregnancy unless there are compelling reasons. There is inadequate evidence of 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

Dosulepin may cause drowsiness in some patients, if this occurs it is advisable not to drive or operate machinery.

4.8 Undesirable effects

The following adverse effects, although not necessarily all reported with dosulepin hydrochloride have occurred with other tricyclic antidepressants, Atropine-like side effects are common early in treatment, but usually lessen as treatment continues.

Class effects
Epidemiological studies, mainly conducted 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 this risk is unknown.

Blood and lymphatic system disorders:
Rare: Bone marrow depression, thrombocytopenia, leucopenia, agranulocytosis, eosinophilia

Immune system disorders:
Hypersensitivity reactions (see Skin and subcutaneous tissue disorders)

Metabolism and nutrition disorders:
Hyponatraemia (usually in the elderly and possibly due to inappropriate secretion of antidiuretic hormone) has been associated with all types of antidepressants and should be considered in all patients who develop drowsiness, confusion or convulsions while taking an antidepressant.

Increased appetite, weight gain, blood sugar concentration changes.

Psychiatric disorders:
Confusion, hypomania, nervousness.
Psychotic manifestations; including mania and paranoid delusions may be exacerbated during treatment with tricyclic antidepressants.

Nervous system disorders:
Drowsiness, tremor, dyskinesia, movement disorders, convulsions (rare), epileptiform seizures, occasional extrapyramidal symptoms including speech difficulties

Eye disorders:
Disturbances of accommodation, raised intraocular pressure.

Cardiac disorders:
Tachycardia, ECG changes including conduction defects, dizziness

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

Vascular disorders:
Postural hypotension, orthostatic hypotension, occasional hypertension

Gastrointestinal disorders:
Dry mouth, constipation, gastric irritation with nausea and vomiting

Hepatobiliary disorders:
Increased liver function test values, cholestatic jaundice, hepatitis (rare)

Skin and subcutaneous tissue disorders:
Rash, urticaria, photosensitivity, purpura, increased sweating, photosensitization

Renal and urinary disorders:
Urinary hesitation

Reproductive system and breast disorders:
Sexual dysfunction, testicular enlargement, gynaecomastia, galactorrhoea

Respiratory disorders
Idiosyncratic alveolitis which may prove fatal

General disorders:
Weakness, fatigue, ataxia, Weight loss may occur as may weight gain and the latter is sometimes associated with inappropriate appetite (carbohydrate craving).

Endocrine disorders:
Inappropriate ADH secretion

Withdrawal symptoms may occur if treatment is ceased abruptly, these include insomnia, irritability, headache, nausea, giddiness, panic-anxiety, extreme motor restlessness and excessive perspiration (see 4.4). Similar symptoms have been reported in neonates whose mothers received tricyclic antidepressants during the third trimester.

In high dosage or in deliberate overdosage, cardiac arrhythmias and severe hypotension are likely to occur. These effects may also occur in patients with pre-existing heart disease taking normal dosage.

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

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Patients ingesting >5mg/kg should seek immediate medical attention.
All children ingesting dosulepin should be assessed by a physician.
Onset of toxicity occurs within 4-6 hours.

Symptoms of overdose
Signs of overdosage are dryness of the mouth, ataxia, drowsiness, loss of consciousness, muscle twitching, widely dilated pupils, hyperreflexia, sinus tachycardia, hypothermia, visual hallucinations, delirium, urinary retention, paralytic ileus, excitement, restlessness, and respiratory or metabolic acidosis. In severe overdosage, convulsions, myoclonus, hypotension, respiratory or cardiac depression with life threatening cardiac arrhythmias which may even occur after apparent recovery.

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 patient with an impaired airway.
- Blood pressure, pulse and cardiac rhythm should be monitored for at least 6hrs 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

ATC CODE: N06A A16 (non-selective monamine reuptake inhibitors)
Dosulepin hydrochloride is a thio derivative of amitriptyline and is an antidepressant of the tricyclic family.

Dosulepin potentiates the effects of biogenic amines in the brain by inhibition of their reuptake at nerve terminals. Dosulepin is active in inhibiting the reuptake of noradrenaline, 5-hydroxytryptamine (5HT) and dopamine. Dosulepin also reduces and/or down regulates central noradrenaline receptor numbers and reduces noradrenaline-induced cyclic AMP formation in the brain. It inhibits the uptake of 5HT into the platelets. Dosulepin also has some central and peripheral anticholinergic and antihistaminic activity at standard dose levels.

5.2 Pharmacokinetic properties

The following pharmacokinetic parameters were obtained with Dosulepin Hydrochloride Capsules 25mg (n=22, total dose 75mg, 3 capsules): C_{max} 37.6ng/ml, T_{max} 2.18 hours, t½. 20.4 hours, AUD (0-t_{last}) 547ng.h/ml and AUDC 587ng.h/ml.

Dosulepin is extensively metabolised in the liver. Dosulepin and its metabolites are eliminated in urine 50% - 60% and faeces 15%-40%, most of which is first excreted in the bile. The main metabolites are the N-demethylated derivative northiaden (desmethyl-dosulepin) and dosulepin S-oxide. Northiaden S-oxide is also produced.
Some is also excreted in the faeces. Dosulepin has been found in breast milk.

5.3 Preclinical safety data

No data of relevance to the prescriber, which is additional to that included in other sections of the SPC

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tribasic calcium phosphate
Starch maize
Povidone K25
Magnesium stearate
Purified Talc

Tablet coating:
Red dye containing:-
Hypromellose (E464)
Macrogol 400
Ponceau 4R (E124)
Titanium dioxide (E171)
Indigo carmine (E132)
Sunset yellow FCF (E110)

6.2 Incompatibilities

None

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package

6.5 Nature and contents of container

PVC blister with aluminium/PVC child resistant (CR) foil containing 14 or 28 capsules

6.6 Special precautions for disposal

Not applicable

7. MARKETING AUTHORISATION HOLDER

Strides Pharma UK Ltd
Unit 4 Metro Centre
Tolpits Lane
Watford
Hertfordshire
WD18 9SS

8. MARKETING AUTHORISATION NUMBER(S)

PL 13606/0098

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21 February 2002

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26/04/2018