

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dothep 75 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 75 mg Dosulepin Hydrochloride (Dothiepin Hydrochloride).

Excipient: Each tablet contains 115 mg Lactose monohydrate and 1.75 mg Ponceau 4R (E124)

For a full list of excipient, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Red film-coated 8.5 mm normal convex tablets embossed DN/75 on one side and G on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Dothep tablets are indicated in the treatment of symptoms of depressive illness, in particular, where an anti-anxiety effect is required.

4.2 Posology and method of administration

Dothep tablets are administered orally.

Recommended dosage schedules:

Adults: Initially 75 mg/day in divided doses (as capsules) 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 dosage regimen: 25 to 50 mg three times daily or, alternatively, 75 or 150 mg as a single dose at night.

Elderly: 50 – 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

Dothep tablets are contra-indicated in patients with:

Closed angle glaucoma, existing urinary retention, recent myocardial infarction, any degree of heart block or other cardiac arrhythmia's, acute psychoses, severe liver disease, women who are breast-feeding, or patients currently receiving monoamine oxidase inhibitors, or have received these within the previous two weeks.

4.4 Special warnings and precautions for use

Special precautions for use:

Dothiepin should not be used in the treatment of 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 a risk of suicidality, self harm and hostility related to these compounds. This risk cannot be excluded with Dothiepin. In addition, Dothiepin 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).

The elderly are particularly liable to experience adverse reactions to antidepressants, especially agitation, confusion, and postural hypotension. Patients posing a high suicidal risk require close supervision.

Dothiepin should be given only with caution to epileptic patients and to those with cardiovascular disorders.

Its use should be avoided in patients with symptoms suggestive of prostatic hypertrophy and a history of epilepsy. Tricyclic antidepressants potentiate the central nervous depressant action of alcohol. Anaesthetics given during the tri/tetracyclic antidepressant therapy may increase the risk of arrhythmia's and hypotension. If surgery is necessary, the anaesthetist should be informed that a patient is being so treated.

It may be two to four weeks from the start of treatment before there is an improvement in the patient's depression. The patient should be monitored closely during this period. The anxiolytic effect may be observed within a few days of commencing treatment. Initially, Dothiepin may impair alertness; patients likely to drive vehicles or operate machinery should be warned of this possibility.

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

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, although this has not been observed following treatment with Dothiepin. It is recommended that antidepressants should be withdrawn gradually.

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.

Special Warnings:

Dependence – withdrawal symptoms may occur on abrupt cessation of treatment.

Tolerance – not applicable.

4.5 Interaction with other medicinal products and other forms of interaction

Dothiepin should not be given concurrently with monoamine oxidase inhibitors (MAOI's); or within 14 days of stopping such treatment. Dothiepin may alter the pharmacological effects of some concurrently administered drugs, including CNS depressants such as alcohol and narcotic analgesics. The effects of these will be potentiated, as will the effects of adrenaline and noradrenaline.

The hypotensive activity of certain anti-hypertensive agents, e.g. bethanidine, debrisoquine, guanethidine, may be reduced by Dothiepin. It is advisable to review all anti-hypertensive therapy during treatment with Dothiepin.

Anaesthetics given during tri/tetracyclic anti-depressant 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.

Barbiturates may decrease and methyl phenidate may increase the serum concentration of Dothiepin and thus affect its antidepressant action.

4.6 Pregnancy and lactation

There is no evidence as to the safety of Dothiepin in human pregnancy nor is there evidence from animal work that it is free from hazard. It should only be used in pregnancy, in particular, in the first and last trimesters, if there are compelling reasons.

Dothiepin is excreted in breast milk; therefore it is not recommended for use during lactation.

4.7 Effects on ability to drive and use machines

No adverse effects expected.

4.8 Undesirable effects

The following adverse effects, although not all reported with Dothiepin, have occurred with other tricyclic antidepressants.

Atropine-like side effects including dry mouth, disturbances of accommodation, tachycardia, constipation and hesitancy of micturition are common in early treatment, but usually diminish. Other adverse effects include drowsiness, sweating, postural hypotension, tremor and skin rashes. Interference with sexual function may occur.

Serious adverse effects are rare. These include depression of the bone marrow, agranulocytosis, cholestatic jaundice, hypomania and convulsions. Psychotic manifestations, including mania and paranoid delusions may be exacerbated during treatment with tricyclic antidepressants.

Cardiac arrhythmia's and severe hypotension are likely to occur with high dosage or in deliberate overdose. They may also occur in patients with pre-existing heart disease taking a normal dose.

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

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.

4.9 Overdose

There is no specific antidote for Dothiepin. Gastric lavage is recommended. 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 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. Bed rest is advisable, even after recovery.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Dothiepin HCl is a tricyclic antidepressant with actions and uses similar to those of amitriptyline.

5.2 Pharmacokinetic properties

Dothiepin HCl is readily absorbed from the gastrointestinal tract and extensively demethylated by first-pass metabolism in the liver to its primary active metabolite, desmethyldothiepin (nortriaden). Dothiepin is excreted in the urine, mainly in the form of its metabolites; small amounts are also excreted in the faeces. The half-life is approximately 19 – 33 hours.

5.3 Preclinical safety data

No further information available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Povidone
Sodium starch glycolate
Talc
Magnesium stearate

Film coating

Polyvinyl alcohol
Ponceau 4R (E124)
Purified talc
Titanium dioxide (E171)
Lecithin
Xanthan gum
Carnauba wax

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Dothep 75 mg tablets are available in pack sizes of 28, 30, 100, 250 and 500 and are packaged in PVC blisters or polypropylene securitainers.

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

McDermott Laboratories (trading as Gerard Laboratories)
35/36 Baldoyle Industrial Estate
Grange Road
Dublin 13

8 MARKETING AUTHORISATION NUMBER

PA 577/20/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 05 September 1997

Date last renewal: 05 September 2007

10 DATE OF REVISION OF THE TEXT

September 2010