ALPHAPHARM PTY LTD

DOTHEP 75 TABLETS

Tricyclic Anti-depressant

Formula:
Each tablet contains 75 mg dothiepin hydrochloride.

Pharmacology:
Site and mode of action. The mechanism by which dothiepin and all tricyclic antidepressants produce an antidepressant effect is unknown, although the therapeutic site of action is thought to be in the CNS. Dothiepin possesses anticholinergic, antihistamine and central sedative properties. It has been claimed that the cause of depression is associated with a functional abnormality of the biogenic amines, particularly the catechol-amines, in the brain. The tricyclics increase the availability of noradrenaline and 5-hydroxytryptamine at central noradrenergic synapses by inhibiting their uptake from nerve endings.

Pharmacokinetics:
Absorption. Dothiepin is well absorbed from the small intestine. There are substantial interindividual variations in plasma concentrations after a single dose due to the interaction of exogenous and endogenous processes. The relationship between dose and concentration in plasma can be quite dynamic and unpredictable, leading to extremely large interindividual differences in steady state drug concentrations in plasms. After a single oral dose of 150 mg, a maximum concentration of 30.4 ng/ml to 278.8 ng/ml was achieved within 2 to 3 hours.

Distribution. Dothiepin crosses the blood-brain and placental barriers in animals and low concentrations are excreted in breast milk. Studies in the dog and cat have shown maximal concentration after 24 hours in liver, uveal tract of the eye, lung, kidney, pituitary and thyroid in descending order. In dogs the tissue/plasma ratio for uveal tract tissue was 257:1.

Protein binding. Approximately 84% of unchanged drug is bound to serum protein.

Metabolism. Dothiepin is extensively demethylated by first-pass metabolism in the liver to its primary active metabolite, desmethyldothiepin (northiaden). In man, 12 basic metabolites have been found in the urine. Paths of metabolism are thought to include N-demethylation, S-oxidation and glucuronic acid conjugation. There is active enterohepatic circulation in animals but this has not been shown in humans.

Excretion. Dothiepin is excreted in the urine, mainly in the form of its metabolites. Appreciable amounts are also excreted in the faeces. Following a 50 mg labelled dose, 71% is excreted in the urine and faeces within 4 days, with 56% being excreted by the renal route.

Half-life. The elimination half-life is biphasic; the first phase is 15 to 18 hours. Mean whole body elimination half-life is 51 hours.

Indications:
Treatment of major depression including reactive (exogenous) depression associated with anxiety and endogenous depression.

Contraindications:
Tricyclic antidepressants should not be used concomitantly or within 14 days of treatment with monoamine oxidase inhibitors since cerebral excitation followed by coma and dangerous hyperthermia may occur following administration of this combination.

Acute recovery phase following myocardial infarction; tricyclic antidepressants may produce conduction defects and arrhythmias.

Hepatic failure (see **Dosage and Administration:** *With impaired liver or renal function*).

Hypersensitivity to dothiepin.

Warnings:
Electroconvulsive therapy. The hazards of ECT may be increased as dothiepin lowers the convulsive threshold.

Epilepsy. Seizure thresholds may be lowered by the drug.

Elective surgery. Dothiepin should be withdrawn prior to surgery.

Severe depression. Patients with severe depression should be closely supervised during early therapy, a the possibility of suicide using dothiepin exists. There patients should not receive large quantities of the drug.

Manic depressive psychosis. A shift towards the manic phase may be provoked by dothiepin.

Monoamine oxidase inhibitors. Dothiepin should not be prescribed concurrently or within 14 days of treatment with MAOIs (see **Contraindications**). After withdrawal of MAOIs, therapy should be initiated at low doses and gradually increased to the normal range.

Cardiovascular disorders. Dothiepin may provoke conduction defects and arrhythmias, and hence should be used with caution.

Hyperthyroidism or patients being treated with thyroid hormone. These patients should be closely supervised as dothiepin may provoke cardiac arrhythmias or conduction defects.

Glaucoma, urinary retention and concurrent anticholinergic therapy. Dothiepin has an anticholinergic action and may aggravate glaucoma and urinary retention, and potentiate anticholinergics.

Concurrent therapy with sympathomimetic drugs. Tricyclic antidepressants have been reported to produce possibly dangerous potentiation of the effects of sympathomimetic drugs.

Suicidality in Children and Adolescents
- Antidepressants increase the risk of suicidal thinking and behaviour (suicidality) in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders.
- Anyone considering the use of an antidepressant in a child or adolescent for any clinical use must balance the risk of increased suicidality with the clinical need.
- Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior.
- Families and caregivers should be advised to closely observe the patient and to communicate with the prescriber.
- The indication(s) approved in paediatric for the particular drug should be clearly stated / included

Precautions:
Dothiepin may activate latent schizophrenia.

Dothiepin may exaggerate paranoid delusions with or without associated hostility.

Renal or hepatic Impairment: toxic blood levels may develop (see **Dosage and Administration:** *With impaired liver or renal function*).

Impairment of motor co-ordination. Alertness is decreased, and hence ability to drive or operate machinery may be impaired.

Ophthalmological examination: Dothiepin or its metabolites may accumulate in the pigmented area of the eye. Therefore, the eyes should be examined regularly for visual acuity and colour fields checking during prolonged therapy.

Elderly patients: dothiepin should be used with care as confusional states may occur.

The potential for dependency is unknown.

Abrupt withdrawal may produce headache, nausea, convulsions and the possibility of thrombotic episodes.

Drug interactions may occur with several drugs (see Interactions).

Use in Pregnancy: Risk Category: C
Tricyclic antidepressants have not been shown to be associated with an increased incidence of birth defects. However, there is evidence of interference with central monoamine neurotransmission in rats. Care should be taken that there are sound indications for the use of these antidepressant during pregnancy.

Use in Lactation:
Small amounts of dothiepin are excreted in breast milk. The possible effect on the child must be carefully considered if it is necessary to give the drug to nursing mothers.

Interactions:
Alcohol. Dothiepin may potentiate the effect of alcohol. One death has been associated with this combination.

Other drugs. Barbiturates: potentiation of the sedative effect is possible.

Tranquillisers and CNS depressants: potentiation of the sedative effect is possible.

Sympathomimetics: dothiepin may dangerously potentiate the sympathomimetic effect.

Monomine oxidase inhibitors: a potentially lethal interaction can occurs between tricyclic antidepressants and MAOIs (see **Contraindications and Warnings**).

Anticholinergics: anticholinergic effects may be potentiated.

Antihistamines: may be potentiated.

Adverse Reactions:
Adverse reactions occur in about 30% of patients. In 10% of patients, the reactions may be severe enough to discontinue the drug.

More common reactions.
Central nervous system, neuromuscular. Drowsiness, extrapyramidal symptoms, tremor, confusional states, disorientation, dizziness, paraesthesia, alterations to EEG patterns.

Anticholinergic. Dry mouth, sweating, urinary retention.

Cardiovascular. Hypotension, tachycardia, palpitations, arrhythmias, conduction defects.

Endocrine. Increased or decreased libido in either sex.

Gastrointestinal. Nausea, vomiting, constipation.

Ocular. Disturbance of accommodation (blurred vision).

Several of the following reactions have been reported with other antidepressants, but should be borne in mind because of their similarity to dothiepin.

Less common reactions.
Central nervous system, neuromuscular. Disturbed concentration, delusions, hallucinations, anxiety, fatigue, headaches, restlessness, excitement, insomnia, nightmares, peripheral neuropathy, ataxia, incoordination, seizures.

Anticholinergic. Paralytic ileus.

Cardiovascular. Hypertension, heart block, myocardial infarction, stroke.

Endocrine. Males: gynaecomastia, testicular swelling, impotence; females: galactorrhoea.

Gastrointestinal. Epigastric distress, abdominal cramps, parotid swellings, diarrhoea, stomatitis, black tongue, peculiar taste sensations.

Haematological. Bone marrow depression including thrombocytopenia, eosinophilia, agranulocytosis.

Hepatic. Cholestatic jaundice, altered liver function.

Allergic. Skin rash, urticaria, photosensitisation, skin blisters, angioneurotic oedema.

Other. Weight loss, urinary frequency, mydriasis. Increased appetite and weight gain have been reported.

Dosage and Administration:
Note. Dosage should be reduced to the smallest amount necessary to maintain relief of the symptoms of depression, once a satisfactory response has been obtained. Plasma levels will reach a new steady state 10 to 14 days after each up or down adjustment.

Adults: Being with 25 mg three times daily for one to two weeks. The daily dosage should be increased by 25 to 50 mg at intervals of one to two weeks it the response is inadequate. The daily dose should not exceed 200 mg.

Up to 150 mg of the daily dose may be given as a single night time dose once an effective dose has been established.

Paediatric: Not recommended for use in children under 16 years since safety and efficacy in this age group has not been established.

Geriatric: Use adult dosage with care particularly in patients with impaired liver or renal function (see below) or cardiovascular disorders (see Warnings).

With impaired liver or renal function: Dothiepin is contraindicated in hepatic failure.

Reduce the dosage and use with caution in patients with impaired liver or renal function since toxic blood levels may develop. Dothiepin is extensively metabolised by the liver, is thought to undergo enterohepatic circulation and its metabolites are excreted in the urine.

Overdosage:
Symptoms: The toxicity of tricyclic antidepressants is attributed mainly to their anticholinergic effects which produce dry mouth, blurred vision, mydriasis, ileus and urinary retention. Common CNS symptoms are agitation, delirium, hyperpyrexia, convulsions, ataxia, respiratory depression and coma. Cardiovascular symptoms include cyanosis, shock, hypotension, tachycardia and cardiac arrhythmias which are often the cause of death.

Individual response is variable, such that death has resulted from overdosage with 0.75 to 1 g of dothiepin, but recovery has occurred after as much as 2 g.

In children, serious overdosage with tricyclic antidepressants occurs more easily with a relatively small total dosage because the dose per weight ratio is higher.

Treatment: Gastric lavage. Induce emesis with syrup of ipecacuanha. In the unconscious patient with no cough reflex, protect the lungs with a cuffed endotracheal tube. As dothiepin is thought to undergo enterohepatic circulation, repeated aspiration may be of benefit by removing the drug and its metabolites excreted into the gut via the bile.

Since the absorbed drug rapidly enters the tissue compartment and is very slowly eliminated, haemodialysis is not recommended. (Whole body elimination half-life = 51 hours.)

General support of the circulation and respiration may be necessary. ECG monitoring is required until a normal ECG and level of consciousness for at least 24 hours is attained. However, prolonged ECG monitoring may be justified in individuals who have taken antidepressants for long periods of time. Xylocaine may be useful in controlling arrhythmias.

Convulsions may be controlled with diazepam. Barbiturates should be avoided due to their respiratory depressant effects, especially if the patient is thought to have been on MAOIs or if barbiturates have been taken in association with the antidepressant in the overdose.

Advice to be Given to Patients:
The main dose should be taken at night as this drug may produce drowsiness.

Ability to drive or operate machinery maybe impaired (see **Precautions**).

Do not discontinue the drug abruptly (see **Precautions**).

Warn patient about OTC preparations containing sympathomimetic drugs particularly patent cold remedies, cough syrups, weight reducing tablets and sedatives/ antihistamines (see **Warnings**).

Presentation:
Dothep 75 75 mg tablet: red film coated, normal convex, marked DT/75 on one side, α on reverse.

Pack Sizes:
Blister packs 30's

Route of administration:
Oral.

Storage Conditions & Shelf Life:
The Shelf life for Dothep 75 is 30 months when stored below 30°C. Protect from moisture, freezing and excessive heat.

Manufactured by:
Alphapharm Pty. Ltd.,
Cnr. Garnet and Antimony Streets
Carole Park 4300
Brisbane, Queensland
Australia

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