

DOSULEPIN MYLAN



1. NAME OF THE MEDICINE

Dosulepin (dothiepin) hydrochloride

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 25 mg of dosulepin (dothiepin) hydrochloride as the active ingredient.

Each tablet contains 75 mg of dosulepin (dothiepin) hydrochloride as the active ingredient.

Dosulepin Mylan 25 capsules contain the following inactive excipients: lactose, povidone, sodium starch glycollate, lactose monohydrate, purified talc, magnesium stearate, purified water, colloidal anhydrous silica, iron oxide red, sodium lauryl sulfate, gelatin, quinoline yellow, titanium dioxide, brilliant blue FCF and erythrosine.

Dosulepin Mylan 75 tablets contain the following inactive excipients: lactose, povidone, maize starch, sodium starch glycollate, purified talc, magnesium stearate, isopropyl alcohol, purified water and Opadry Red OY-B-25005.

3. PHARMACEUTICAL FORM

DOSULEPIN MYLAN 25 mg capsule: hard capsule with green body and red cap.

DOSULEPIN MYLAN 75 mg tablet: red, normal convex film coated tablet, marked “DT/75” on one side, and “α” on reverse.

Dothiepin hydrochloride is a white or faintly yellow, crystalline powder. It is freely soluble in water, in alcohol and in methylene chloride. The partition coefficient (log p) for dothiepin hydrochloride is 4.98 and the pKa is 9.76.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

For the treatment of major depression.

The 75 mg tablet is indicated only for the maintenance treatment of major depression (see **Section 4.4. Special Warning and Precautions for Use**).

4.2. DOSE AND METHOD OF ADMINISTRATION

The main dose should be taken at night as it may produce drowsiness.

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

Begin 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 if 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.

Use in Children and Adolescents (<18 years)

The safety and efficacy of Dosulepin Mylan for the treatment of depression or other psychiatric disorders in children and adolescents aged less than 18 years has not been satisfactorily established. Dosulepin Mylan should not be used in this age group for the treatment of depression.

Use in the Elderly

Use adult dosage with care particularly in patients with impaired liver or renal function (see below) or cardiovascular disorders (see **Section 4.4. Special Warning and Precautions for Use**).

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.

4.3. CONTRAINDICATIONS

Epilepsy; seizure thresholds may be lowered by the drug.

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 anti-depressants may produce conduction defects and arrhythmias.

Hepatic failure (see **Section 4.2 Dose and Method of Administration: With impaired liver or renal function**).

Hypersensitivity to dothiepin.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Due to its toxicity in overdose, Dosulepin Mylan should only be used in patients intolerant of or unresponsive to alternative treatment options (See **Section 4.9. Overdose**).

Toxicity in overdose

Dothiepin 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 that may increase the risk of toxicity associated with dothiepin (see **Section 4.5. Interactions with Other Medicines and Other Forms of Interactions**).

- Patients should be advised to store the medicine securely, out of sight and reach of children.
- In cases of overdose, patients should seek IMMEDIATE MEDICAL ATTENTION (see **Section 4.9. Overdose**).

Clinical Worsening and Suicide Risk associated with Psychiatric Disorders

The risk of suicide attempt is inherent in depression and may persist until significant remission occurs. This risk must be considered in all depressed patients.

Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviour (suicidality), whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored for clinical worsening and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality symptoms that may be precursors to worsening depression or suicidality, if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Patients with co-morbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behaviour (suicidality) in children, adolescents and young adults (aged 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

Pooled analyses of 24 short-term (4 to 16 weeks), placebo-controlled trials of nine antidepressant medicines (SSRIs and others) in 4400 children and adolescents with major depressive disorder (16 trials), obsessive compulsive disorder (4 trials), or other psychiatric disorders (4 trials) have revealed a greater risk of adverse events representing suicidal behaviour or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients treated with an antidepressant was 4%, compared with 2% of patients given placebo. There was considerable variation in risk among the antidepressants, but there was a tendency towards an increase for almost all antidepressants studied. The risk of suicidality was most consistently observed in the major depressive disorder trials, but there were signals of risk arising from trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in these trials. It is unknown whether the suicidality risk in children and adolescent patients extends to use beyond several months. The nine antidepressant medicines in the pooled analyses included five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and four non-SSRIs (bupropion, mirtazapine, nefazodone, venlafaxine).

Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adults and paediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric. Although a causal link between the emergence of such symptoms and either worsening of depression and/or emergence of suicidal impulses has not been established, there is concern that such symptoms may be precursors of emerging suicidality.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and non-psychiatric, should be alerted about the need to monitor these patients for the emergence of agitation, irritability, unusual changes in behaviour, and other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers.

Prescriptions for Dosulepin Mylan should be written for the smallest quantity of tablets or capsules consistent with good patient management, in order to reduce the risk of overdose.

Latent schizophrenia may be activated by dothiepin.

Psychotic manifestations, including mania and paranoid delusions, with or without associated hostility, may be exaggerated during treatment with tricyclic antidepressants.

Screening Patients for Bipolar Disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

Dosulepin Mylan 75 mg Tablets

The 75 mg tablets are indicated only for the maintenance treatment of major depression. The 75 mg tablets should not be used in acutely ill patients where there is a risk of suicide. There is an increased risk of completed suicide by overdose with the 75 mg tablet compared with the 25 mg capsule.

Electroconvulsive therapy (ECT)

The hazards of ECT may be increased as dothiepin lowers the convulsive threshold.

Elective surgery

Dothiepin should be withdrawn prior to surgery as anaesthetics given during tricyclic antidepressant therapy may increase the risk of arrhythmias and hypotension.

Severe depression

Patients with severe depression should be closely supervised during early therapy, as the possibility of suicide using dothiepin exists. These 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 **Section 4.3. Contraindications**). After withdrawal of MAOIs, therapy should be initiated at low doses and gradually increased to the normal range.

Cardiovascular disorders

Dosulepin Mylan 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 Mylan in the elderly and in patients with suspected cardiovascular disease (see **Section 4.3. Contraindications**).

Hyperthyroidism or patients being treated with thyroid hormone

These patients should be closely supervised as dothiepin may provoke cardiac arrhythmias or conduction defects.

Glaucoma, prostatic hypertrophy, 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 anti-depressants have been reported to produce possibly dangerous potentiation of the effects of sympathomimetic drugs.

Use in renal or hepatic impairment

Use with care as toxic blood levels may develop (see **Section 4.2. Dose and Method of 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 checked during prolonged therapy.

Use in the Elderly

Dothiepin should be used with care as confusional states may occur.

Dependence and Withdrawal

The potential for dependency is unknown.

Abrupt withdrawal may produce headache, nausea, convulsions, insomnia, irritability, excessive perspiration and the possibility of thrombotic episodes. It is recommended that antidepressants be withdrawn gradually. Symptoms similar to insomnia, irritability and excessive perspiration have also been reported in neonates whose mothers received tricyclic antidepressants during the third trimester.

Paediatric Use

The safety and efficacy of Dosulepin Mylan for the treatment of depression or other psychiatric disorders in children and adolescents aged less than 18 years has not been satisfactorily established. Dosulepin Mylan should not be used in this age group for the treatment of depression or other psychiatric disorders.

Effects on laboratory tests

No interference reported with laboratory tests.

Advice to be given to Patients

The main dose should be taken at night as this drug may produce drowsiness.

Do not discontinue the drug abruptly.

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

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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.

Guanethidine and other adrenergic neurone blocking drugs: dothiepin may block the antihypertensive effect.

Sympathomimetics: dothiepin may dangerously potentiate the sympathomimetic effect.

Monoamine oxidase inhibitors: a potentially lethal interaction can occur between tricyclic antidepressants and MAOIs (see **Section 4.3. Contraindications** and **Section 4.4. Special Warnings and Precautions for Use**).

Anticholinergics: anticholinergic effects may be potentiated.

Antihistamines: may be potentiated.

Diuretics: there is an increased risk of postural hypotension when tricyclic antidepressants are given with diuretics.

Antiepileptics: tricyclic antidepressants may also antagonize the anticonvulsant effect of antiepileptics (convulsive threshold decreased).

Food

No information available.

4.6. FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No information available.

Use in pregnancy (Category C)

Withdrawal symptoms in newborn infants have been reported with prolonged maternal use of this class of drugs.

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 antidepressants during pregnancy. (See also **Section 4.4. Special Warnings and Precautions for Use: Dependence and Withdrawal**).

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 breastfeeding mothers.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Because alertness is decreased whilst using Dosulepin Mylan, the ability to drive or operate machinery may be impaired.

4.8. ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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

More common effects

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, postural 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 not yet been reported with dothiepin, but should be borne in mind because of its similarity to other antidepressants.

Less common effects

Central nervous system, neuromuscular. Disturbed concentration, delusions, hallucinations, anxiety, fatigue, headaches, restlessness, excitement, insomnia, hypomania, 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, hepatitis.

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

Other. Weight loss, urinary frequency, mydriasis. Increased appetite and weight gain have been reported but it is not known whether they are due to relief of depression or to the drug.

Adverse events have been reported during post-approval use of dothiepin. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to dothiepin exposure.

Table 1: Additional Adverse Effects from Postmarketing Surveillance

System Organ Class	Adverse Reaction
Immune system disorders	Hypersensitivity reactions
Endocrine disorders	Endocrine side effects
Metabolism and nutrition disorders	Hyponatremia
Nervous system disorders	Movement disorders
Investigations	Increased intraocular pressure, changes in blood sugar levels
Gastrointestinal disorders	Dyspepsia

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at <http://www.tga.gov.au/reporting-problems>.

4.9. OVERDOSE

The onset of toxicity occurs within 4-6 hours.

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

All children ingesting Dosulepin Mylan should be assessed by a physician.

Symptoms

The toxicity of tricyclic antidepressants is attributed mainly to their anticholinergic effects which produce dry mouth, blurred vision, mydriasis, paralytic ileus and urinary retention.

Common CNS symptoms are agitation, delirium, hyperpyrexia, convulsions, ataxia, respiratory depression, coma, unconsciousness, muscle twitching, hyperreflexia, hypothermia, visual hallucinations and respiratory or metabolic alkalosis.

Cardiovascular symptoms include cyanosis, shock, hypotension, sinus tachycardia and cardiac arrhythmias, which are often the major cause of death.

Individual response is variable, e.g. death has resulted from overdosage with 0.75 to 1 g of dothiepin (30 to 40 capsules), but recovery has occurred after as much as 2 g (80 capsules).

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

Management

- A clear airway and adequate ventilation should be ensured. Hypoxia and acid-based imbalances should be corrected by assisted ventilation and intravenous 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.
- 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 anti-arrhythmic agents as these may exacerbate the arrhythmia.
- In cases of cardiac arrest, persist with prolonged CPR (for at least 1 hour).
- Convulsions should be controlled with intravenous diazepam or lorazepam.
- Due to their respiratory depressant effects, barbiturates should be avoided 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.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Mechanism of action

Dothiepin is a thioanalogue of amitriptyline. It is generally equivalent to amitriptyline in antiserpine activity but less potent than imipramine.

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 catecholamines, in the brain. The tricyclics increase the availability of noradrenaline and 5-hydroxytryptamine at central noradrenergic synapses by inhibiting their uptake from nerve endings.

Clinical trials

No data available.

5.2. PHARMACOKINETIC PROPERTIES

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 plasma. 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, desmethylclothiepin (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.

5.3. PRECLINICAL SAFETY DATA

No data available.

6. PHARMACEUTICAL PROPERTIES

6.1. LIST OF EXCIPIENTS

Refer to Section 2-Qualitative and quantitative composition.

6.2. INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3. SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Dosulepin Mylan 25 Store below 25°C

Dosulepin Mylan 75 Store below 30°C.

6.5. NATURE AND CONTENTS OF CONTAINER

Dosulepin Mylan 25, 25 mg capsule: PVC/PVdc/Aluminium blister pack of 50's.

Dosulepin Mylan 75, 75 mg tablet: PVC/PVdc/Aluminium blister pack of 30's.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

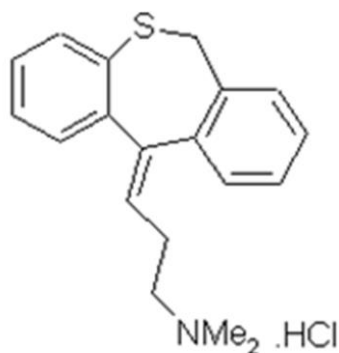
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7. PHYSIOCHEMICAL PROPERTIES

Chemical structure

Chemical name: *(E)*-3-(Dibenzo[*b,e*]thiepin-11(6*H*)-ylidene)-*N,N*-dimethylpropan-1-amine hydrochloride (1:1)

Structural formula:



Molecular formula: C₁₉H₂₁NS.HCl

Molecular Weight: 331

CAS number

177036-94-1

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8. SPONSOR

Alphapharm Pty Limited

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Millers Point NSW 2000

www.mylan.com.au

9. DATE OF FIRST APPROVAL

23/08/2017

10. DATE OF REVISION

04/06/2018

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new Information
<i>All</i>	<i>Editorial changes in line with new Product Information format.</i>
<i>Various</i>	<i>Minor editorial changes to be in line with approved Dosulepin Mylan PI</i>