

DOSULEPIN MYLAN



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## 1. Product Name

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DOSULEPIN MYLAN, 75 mg film-coated tablets.

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## 2. Qualitative and Quantitative Composition

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Each DOSULEPIN MYLAN 75 mg film-coated tablet contains 75 mg of dosulepin (dothiepin) hydrochloride.

DOSULEPIN MYLAN tablets contain lactose. For the full list of excipients, see section 6.1.

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## 3. Pharmaceutical Form

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DOSULEPIN MYLAN 75 mg tablets: 8.5 mm, normal, convex, red, film-coated tablet debossed "DT/75" on one side and "α" on the other.

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## 4. Clinical Particulars

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### 4.1 *Therapeutic indications*

Depression of any aetiology and the anxiety frequently associated with depressive illness.

### 4.2 *Dose and method of administration*

#### **Dose**

##### **Adults**

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

##### **Elderly**

50-75 mg daily initially. Half the normal adult dose may be sufficient to produce a satisfactory clinical response.

##### **Adolescents**

Not recommended for use in adolescent patients 13-18 years of age for the treatment of depression, unless under the supervision of a specialist.

### 4.3 *Contraindications*

- Dosulepin is contraindicated for the treatment of depression in patients 12 years of age and under.
  - Dosulepin is contraindicated for the treatment of nocturnal enuresis.
  - Epilepsy; seizure thresholds may be lowered by the medicine.
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- Tricyclic antidepressants should not be used concomitantly or within 14 days of treatment with MAOIs since the combination may cause cerebral excitation followed by coma and dangerous hyperthermia.
- Acute recovery phase following myocardial infarction; tricyclic antidepressants may produce conduction defects and arrhythmias.
- Hepatic failure.
- Hypersensitivity to dosulepin or to any of the excipients listed in section 6.1.

#### **4.4 Special warnings and precautions for use**

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

##### **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 75 mg/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 dosulepin (see section 4.5).
- Patients should be advised to store the medicines securely, out of sight and reach of children.
- In cases of overdose, patients should seek IMMEDIATE MEDICAL ATTENTION (see section 4.9).

##### **Clinical worsening and suicide risk**

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 of any age with Major Depressive Disorder may experience worsening of their depression 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 therapy or when the dose is changed, until such improvement occurs.

There has been a long-standing concern that some antidepressants may have a role in the emergence of suicidality in some patients. The possible risk of increased suicidality in patients applies to all classes of antidepressant medicines, as available data are not adequate to exclude this risk for any antidepressant. Therefore, 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. Generally, when stopping an antidepressant, doses should be tapered rather than stopped abruptly.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult 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 the worsening of depression and/or the emergence of suicidal impulses has not been established, consideration should be given

to changing the therapeutic regimen, including possibly discontinuing the medication, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and non-psychiatric disorders, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric and non-psychiatric disorders.

Latent schizophrenia may be activated by dosulepin.

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

### **Mania and 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 any antidepressant alone may increase the likelihood of a mixed/manic episode in patients at risk for bipolar disorder. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that dosulepin is not approved for use in treating bipolar depression.

### **Information for patients and families**

Patients and their families should be alerted about the need to monitor for the emergence of anxiety, agitation, panic attacks, insomnia, irritability, unusual changes in behaviour, hostility, impulsivity, akathisia, hypomania, mania, worsening of depression, and suicidal ideation, especially early during antidepressant treatment. Such symptoms should be reported to the patient's doctor, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Such monitoring should include daily observation by families and caregivers.

*The patient has the right to treatment meeting appropriate ethical and professional standards, and the patient needs to be fully informed with frank discussion of risk/benefit issues relating to the medicines efficacy and safety when used in the treatment regimen proposed.*

### **Electroconvulsive therapy**

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

### **Elective surgery**

The medicine 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 dosulepin exists. These patients should not receive large quantities of the drug.

### **Manic depressive psychosis**

A shift towards the manic phase may be provoked by dosulepin.

### **Monoamine oxidase inhibitors**

Do not prescribe dosulepin concurrently or within 14 days of treatment with MAOIs (see section 4.3). After withdrawal of MAOIs, initiate therapy at low doses and gradually increase to the normal range.

## **Cardiovascular disorders**

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).

Use with caution in patients with severe cardiovascular disease, including heart failure, conduction disorders (e.g. AV block grades I to III) or cardiac arrhythmia. Cardiovascular and ECG monitoring should be undertaken in such patients. An ECG should be performed prior to starting treatment, at steady state, after an increase in dose or after starting any potentially interacting medicine.

Tricyclic antidepressant medicines, including dosulepin, particularly when given in high doses, have been reported to produce QTc prolongation, arrhythmias (including Torsades de Pointes (TdP), sinus tachycardia, and prolongation of the conduction time). Myocardial infarction and stroke have been reported with medicines of this class (see section 4.8).

Dosulepin should be used with caution in patients with risk factors for QTc prolongation/TdP including congenital long QT syndrome, age >65 years, female sex, structural heart disease/LV dysfunction, medical conditions such as renal or hepatic disease, use of medicines that inhibit the metabolism of dosulepin, and the concomitant use of other QTc prolonging medicines (see section 4.5). Hypokalaemia and hypomagnesaemia should be corrected prior to treatment.

Consideration should be given to stopping dosulepin treatment or reducing the dose if the QTc interval is >500ms or increases by >60ms.

## **Hyperthyroidism or patients being treated with thyroid hormone**

Closely supervise these patients as the medicine may provoke cardiac arrhythmias or conduction defects.

## **Glaucoma, prostatic hypertrophy, urinary retention and concurrent anticholinergic therapy**

Dosulepin has an anticholinergic action and can exacerbate glaucoma and urinary retention and potentiate anticholinergics.

## **Concurrent therapy with sympathomimetic medicines**

Tricyclic antidepressants have been reported to produce possible dangerous potentiation of the effects of sympathomimetic medicines.

## **Renal or hepatic impairment**

Use with care as toxic blood levels may develop.

## **Ophthalmological examination**

Dosulepin 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.

## **Impairment of motor co-ordination**

Ability to drive or operate machinery may be impaired as alertness is decreased.

## **Use in the elderly**

Use with care as confusional states may occur.

## **Dependence and withdrawal**

Dependency potential 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 in neonates whose mothers received tricyclic antidepressants during the third trimester also have been reported.

### **Instructions to patients**

Ability to drive or operate machinery may be impaired.

Do not abruptly discontinue the medicine.

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

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

### **Interference with Laboratory Tests**

No interference reported with laboratory tests.

## **4.5 Interaction with other medicines and other forms of interaction**

### **Alcohol**

The effect of alcohol may be potentiated by dosulepin. One death has been associated with this combination.

### **Medicines that can prolong the QT interval**

The risk of QTc prolongation and/or ventricular arrhythmias (e.g. Torsades de Pointes) is increased with concomitant use of other medicines which prolong the QTc interval (e.g. some antipsychotics and antibiotics). Please check the data sheet of other medicines administered for information on their effects on the QTc interval.

### **Other drugs**

#### ***Barbiturates***

The sedative effect may be potentiated.

#### ***Tranquillisers and CNS depressants***

The sedative effect may be potentiated.

#### ***Guanethidine and other adrenergic neurone blocking drugs***

The antihypertensive effect may be blocked by dosulepin.

#### ***Sympathomimetics***

The sympathomimetic effect may be dangerously potentiated by dosulepin.

#### ***Monoamine oxidase inhibitors***

A potentially lethal interaction can occur between MAOIs and tricyclic antidepressants (see sections 4.3 and 4.4).

#### ***Anticholinergics***

Dosulepin may potentiate their anticholinergic effects.

#### ***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 antagonise the anticonvulsant effect of antiepileptics (convulsive threshold decreased).

### **Food**

No information available.

## **4.6 Fertility, pregnancy and lactation**

### **Pregnancy**

Category C.

Dosulepin should only be used in pregnancy if considered necessary, taking into account the risks of untreated depression, and under the close supervision of a physician.

Epidemiological studies have suggested an increased risk of congenital abnormalities associated with use of tricyclic antidepressants in pregnancy. There is evidence of interference with central monoamine neurotransmission in rats.

Neonates should be observed if maternal use of dosulepin has continued into the later stages of pregnancy, particularly into the third trimester.

Neonates exposed to tricyclic antidepressants, late in the third trimester have showed drug withdrawal symptoms such as dyspnoea, lethargy, colic irritability, hypotension or hypertension and tremor or spasms.

Epidemiological data suggests that the use of tricyclic antidepressants in pregnancy may be associated with an increase in pre-term delivery.

### **Breast-feeding**

Small amounts of dosulepin have been observed in breast milk and its possible effect on the child must be carefully considered if it is necessary to give the medicine to breastfeeding mothers.

### **Fertility**

No data available.

## **4.7 Effects on ability to drive and use machines**

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

## **4.8 Undesirable effects**

These occur in about 30% of patients and may be severe enough to discontinue the medicine in 10% of patients.

### **More common reactions**

#### **Central nervous system, neuromuscular**

Drowsiness, dizziness, tremor, extrapyramidal symptoms, confusional states, paraesthesia, alterations to EEG patterns, disorientation.

**Anticholinergic**

Dry mouth, urinary retention, sweating.

**Cardiovascular**

Hypotension, postural hypotension, tachycardia, arrhythmias (including ventricular tachycardia, ventricular fibrillation and Torsades de Pointes), conduction defects, palpitations.

**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 dosulepin but must be borne in mind because of its similarity to other antidepressants.

**Less common reactions****Central nervous system, neuromuscular**

Disturbed concentration, delusions, hallucinations, excitement, anxiety, hypomania, restlessness, insomnia, nightmares, peripheral neuropathy, ataxia, incoordination, seizures, fatigue, headaches.

**Anticholinergic**

Paralytic ileus.

**Cardiovascular**

Hypertension, myocardial infarction, stroke, syncope, ECG changes (including QTc prolongation, non-specific ST and T wave changes, and AV conduction disorders such as heart block, bundle branch block and widened QRS complex).

**Endocrine**

*Males:* Gynaecomastia, testicular swelling, impotence; *Females:* Galactorrhoea.

**Gastrointestinal**

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

**Haematological**

Bone marrow depression including agranulocytosis, thrombocytopenia, eosinophilia.

**Hepatic**

Cholestatic jaundice, hepatitis, altered liver function.

**Allergic**

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

**Other**

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

Adverse events have been reported during post-approval use of dosulepin. 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 dosulepin exposure.

<b>System organ class</b>	<b>Adverse effect</b>
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

### **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.

### **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

## **4.9 Overdose**

The onset of toxicity occurs within 4-6 hours.

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

All children ingesting dosulepin should be assessed by a physician.

### **Symptoms**

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

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

Cardiovascular symptoms include cyanosis, hypotension, shock, tachycardia, cardiac arrhythmias (including Torsades de Pointes) which are often the major cause of death, QTc prolongation, conduction disorders, shock, heart failure; and in very rare cases cardiac arrest.

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

In children, serious overdose 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 an 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 further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

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## 5. Pharmacological Properties

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### 5.1 *Pharmacodynamic properties*

Pharmacotherapeutic group: antidepressants, ATC code: N06AA16

#### **Mechanism of action**

Dosulepin (dothiepin) hydrochloride is a tricyclic antidepressant. It is a thioanalogue of amitriptyline. In antiserpine activity it is generally equivalent to amitriptyline but less potent than imipramine.

The therapeutic site of action is thought to be in the CNS, but the mechanism by which this medicine and all tricyclic antidepressants produce an antidepressant effect is unknown. Dosulepin possesses anticholinergic, antihistamine and central sedative properties. It has been claimed that the cause of depression is associated with a functional abnormality of one or more of the biogenic amines, particularly the catecholamines, in the brain. The tricyclics inhibit uptake of noradrenaline and 5-hydroxytryptamine from the nerve endings thus increasing their availability at central noradrenergic synapses.

### 5.2 *Pharmacokinetic properties*

#### **Absorption**

Dosulepin is well absorbed from the small intestine. There are substantial inter-individual variations in plasma concentrations after a single dose and concentration in plasma can be quite dynamic and unpredictable, leading to extremely large inter-individual differences in steady state drug concentrations in plasma. After a single oral dose of 150 mg, a maximum concentration of 30.4 nanogram/mL to 278.8 nanogram/mL was achieved within 2 to 3 hours. Steady state concentrations appear to be reached after 10 to 14 days.

#### **Distribution**

Unchanged drug is about 84% bound to serum protein.

#### **Biotransformation**

Dosulepin 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.

## **Elimination**

Dosulepin 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.

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

### **5.3 Preclinical safety data**

Dosulepin is present in low concentrations in breast milk. It crosses the placental and blood-brain barriers in animals. Animal studies in the dog and cat show 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.

There is active enterohepatic circulation in animals but this has not been shown in humans.

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## **6. Pharmaceutical Particulars**

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### **6.1 List of excipients**

DOSULEPIN MYLAN 75 mg tablets also contain:

- lactose
- maize starch
- povidone
- purified talc
- sodium starch glycollate
- magnesium stearate
- polyvinyl alcohol
- colourant ponceau 4R lake
- talc
- titanium dioxide
- lecithin soya
- xanthan gum.

DOSULEPIN MYLAN is gluten free.

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years.

### **6.4 Special precautions for storage**

Store at or below 30°C.

### **6.5 Nature and contents of container**

Blister pack of 30 or 100 tablets.

### **6.6 Special precautions for disposal**

Not applicable.

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## 7. Medicines Schedule

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Prescription Medicine

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## 8. Sponsor Details

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Mylan New Zealand Ltd  
PO Box 11183  
Eilerslie  
AUCKLAND  
Telephone 09-579-2792

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## 9. Date of First Approval

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22 September 1989

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## 10. Date of Revision of the Text

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7 January 2019

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### Summary table of changes

Section	Summary of new information
All	Trade name changed to Dosulepin Mylan
All	Separated 25 mg strength from data sheet
3	Change to tablet description
6.1	Change to film coating colourant
6.4	Storage condition increased to 30°C
6.5	Additional 30's pack size