

# NEW ZEALAND DATA SHEET

## DOPRESS

*Dosulepin (dothiepin) 25mg Capsules  
and 75mg Tablets*



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## Presentation

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DOPRESS 25 mg capsules: Brown OP body, Scarlet OP cap, size 4, containing a white powder. Each capsule contains 25 mg dothiepin (dosulepin) hydrochloride.

DOPRESS 75 mg tablets: Dark red, film coated biconvex tablets, 11/32" diameter, imprinted DN75 on one side. Each tablet contains 75 mg dothiepin (dosulepin) hydrochloride.

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## Uses

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### **Actions**

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

### **Site and Mode of Action**

The 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 is postulated that the aetiology 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.

### **Pharmacokinetics**

#### **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. In 10 patients taking 100 mg/day for two weeks, the serum concentration ranged from 18 to 84 nanogram/mL (mean  $41 \pm 7$  nanogram/mL). After increasing the dose to 175 mg/day for a further two weeks the concentration ranged from 43 to 196 nanogram/mL (mean  $96 \pm 15$  nanogram/mL). 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**

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.

#### **Protein Binding**

Unchanged drug is about 84% bound to serum protein.

#### **Metabolism**

Dosulepin is metabolised in the liver and in man 12 basic metabolites were found in the urine, the bulk of which are northiaden sulphoxide and dosulepin sulphoxide. The metabolic pathways are thought to consist of N-demethylation, S-oxidation and glucuronic acid conjugation. There is active enterohepatic circulation in animals but this has not been studied in humans.

## **Excretion**

71% of a 50mg labelled dose is excreted in the urine and faeces within 4 days, 56% being by the renal route.

## **Half-life**

The elimination half-life is biphasic; the first phase is 15 hours, the second 56 hours. Mean whole body elimination half-life is 51 hours.

## **Indications**

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

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## **Dosage and Administration**

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### **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.

### **Adolescent Depression**

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

### **Instructions to Patients**

The main dose may be taken at night as it may produce drowsiness. 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 and weight reducing tablets.

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## **Contraindications**

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- 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.
  - 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.
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## **Warnings and Precautions**

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

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## 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 Interactions)
- 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 Overdosage).

## Clinical Worsening and Suicide Risk

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. Patients should be closely monitored, 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 whose emergent suicidality is severe, abrupt in onset, or was 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, 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.

*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.

### **Monoamine Oxidase Inhibitors**

Do not prescribe dosulepin concurrently or within 14 days of MAOIs (see Contraindications). 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 Contraindications).

### **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**

Eyes should be examined regularly for visual acuity and colour fields checked during prolonged therapy since the medicine or its metabolites may accumulate in the pigmented area of the eye in experimental animals.

### **Impairment of Motor Co-ordination**

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

### **Elderly Patients**

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.

## ***Use in 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.

## ***Use in Lactation***

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.

## ***Effect on Ability to Drive or Operate Machinery***

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

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## **Adverse Effects**

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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, 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, heart block, stroke.

### 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.

**Table1: Additional Adverse Effects from Postmarketing Surveillance**

System Organ Class	Adverse Effect
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

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## Interactions

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### Alcohol

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

### Other drugs

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### **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 Contraindications and Warnings and Precautions).

### **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.

### **Interference with Clinical, Laboratory and Other Tests**

No interference reported with laboratory tests.

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## **Overdosage**

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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, ileus and urinary retention.

Common CNS symptoms are agitation, delirium, ataxia, hyperpyrexia, convulsions, respiratory depression and coma.

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

Individual response varies, e.g. death has resulted from overdosage 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 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-base 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.

In cases of overdosage, it is advisable to contact the National Poisons Information Centre on 0800 POISON or 0800 764 766 for recommendation on the management and treatment of overdosage.

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## Pharmaceutical Precautions

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Store below 25°C.

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## Medicine Classification

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Prescription Medicine.

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## Package Quantities

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DOPRESS 25 mg capsules: Blister packs of 100 capsules.

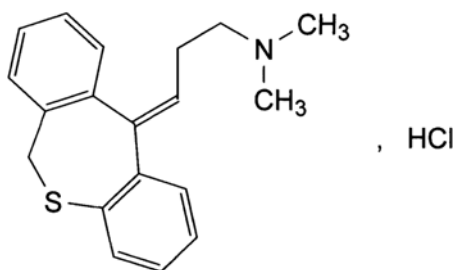
DOPRESS 75 mg tablets: Blister packs of 100 tablets.

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## Further Information

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The active ingredient in Dopress is dosulepin hydrochloride (previously known as dothiepin hydrochloride). The structural formula for dosulepin (dothiepin) hydrochloride is:



Molecular formula: C<sub>19</sub>H<sub>21</sub>NS.HCl

Molecular weight: 331.9

CAS Registry No: 897-15-4

Dosulepin hydrochloride is a white or faintly yellow, crystalline powder. It is freely soluble in water, in alcohol and in methylene chloride.

### ***Excipients***

DOPRESS 25 mg capsules also contain lactose, maize starch, purified talc, colloidal silicon dioxide and magnesium stearate. The capsules shell contains gelatin, titanium dioxide, FD & C red 3, FD & C red 40, FD & C blue 1 and FD & C yellow 6.

DOPRESS 75 mg tablets also contain lactose, maize starch, povidone, purified talc, sodium starch glycollate, magnesium stearate, and film coat of diethyl phthalate, hypromellose, Opaspray Red K-1F-4972 (with colourants titanium dioxide and carmoisine aluminium lake), and carnauba wax as a polishing agent.

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## **Name and Address**

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## **Date of Preparation**

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23 June 2010