1 NAME OF THE MEDICINAL PRODUCT
Dosulepin 75mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains dosulepin hydrochloride 75 mg.

Excipient(s) with known effect
Each tablet contains 140 mg of lactose monohydrate and colourants Sunset Yellow (E110) and Ponceau 4R Red (E124). For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Red, biconvex, film-coated tablets imprinted with ‘MP76’ on side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Dosulepin is indicated in the treatment of symptoms of depressive illness especially where an anti-anxiety effect is required.

Due to its toxicity in overdose, Dosulepin should only be used in patients intolerant of or unresponsive to alternative treatment options (see sections 4.4 and 4.9).

Initiation of treatment for patients who have not previously received Dosulepin should be restricted to specialist care prescribers.

4.2 Posology and method of administration

Posology

Adults
Initially 75 mg/day in divided doses 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 regimens: 25 or 50 mg three times daily or, alternatively, 75 or 150 mg as a single dose at night. Should the regimen of 150 mg as a single night-time dose be adopted, it is better to give a smaller dose for the first few days.
Use in the 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.

It has been found that, in certain cases of depression, the daily dose of dosulepin given as a single night-time dose is more effective and even better tolerated than the conventional divided day-time dosage. There is evidence that this single bed-time dose improves the sleep pattern of the depressed patient.

There may be a latent period of up to two to four weeks from the start of treatment, before any improvement in the patient’s depression occurs.

Paediatric population

Not recommended.

Method of administration

Oral

4.3 Contraindications

Recent myocardial infarction.

Any degree of heart block or other cardiac arrhythmias.

Mania.

Severe liver disease.

Hypersensitivity to the active substance or any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

<table>
<thead>
<tr>
<th>Toxicity in overdose</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
</tr>
<tr>
<td>− 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.</td>
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<tr>
<td>− 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.</td>
</tr>
<tr>
<td>− Avoid concomitant medications which may increase the risk of toxicity associated with dosulepin (See Section 4.5)</td>
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<tr>
<td>− Patients should be advised to store the tablets securely, out of sight and reach of children.</td>
</tr>
<tr>
<td>− In cases of overdose, patients should seek IMMEDIATE MEDICAL ATTENTION (see section 4.9)</td>
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</tbody>
</table>
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).

The elderly are particularly liable to experience adverse reactions to antidepressants, especially agitation, confusion and postural hypotension.

**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.

**Other Special Warnings**

Dosulepin should be given with caution to patients with phaeochromocytoma or porphyria.

Care should be taken where there is a history of mania or psychoses. Dosulepin may aggravate psychotic symptoms. Patients posing a high suicidal risk require close supervision.

Avoid if possible in patients with a history of epilepsy, thyroid disease, mania or urinary retention and in those with hepatic impairment, narrow angle glaucoma or symptoms suggestive of prostatic hypertrophy.

Care should be exercised if a patient receiving treatment undergoes surgery as anaesthetics may increase the risk of arrhythmias or hypotension. If surgery is required the anaesthetist should be informed that the patient is receiving dosulepin treatment.

Concomitant treatment with electroconvulsive therapy should be undertaken only under careful supervision.

Conduction defects or cardiac arrhythmias may occur in hyperthyroid patients.

Toxic levels of dosulepin may develop in patients with severe renal disease.

**Other Precautions for use**

After initiating antidepressant therapy, it may be two to four weeks before there is an improvement in a patient's depression. It is important that the patient is carefully monitored during this period. The anxiolytic effect may be observed within a few days of commencing treatment. Initially, dosulepin may impair alertness; patients likely to drive vehicles or operate machinery should be warned of this possibility.
Hyponatraemia (usually in the elderly and possibly due to an inappropriate section to antidiuretic hormone) has been associated with all types of antidepressants and should be considered in all patients who develop drowsiness, confusion or convulsions while taking an antidepressant (see section 4.8).

Dosulepin treatment should not be stopped suddenly as this can lead to withdrawal symptoms such as insomnia, irritability and sweating (see section 4.8).

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

Patients should be informed that this medicine also contains the colourants ponceau red (E124) and sunset yellow (E110) which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Dosulepin has quinidine-like actions on the heart and concomitant use with other drugs which may affect cardiac conduction should be avoided. There is an increased risk of ventricular arrhythmias when dosulepin is given with anti-arrhythmics (e.g. disopyramide, flecainide, procainamide, propafenone, quinidine, sotalol) or antihistamines (e.g. astemizole, terfenadine). There is also a risk of arrhythmias when dosulepin is given with anti-psychotics (e.g. pimozide) or halofantrine. Adrenaline and noradrenaline when taken with dosulepin may also cause ventricular arrhythmias. Amiodarone taken with dosulepin may also cause arrhythmias. Due to the long half-life of amiodarone there is a potential for interactions to occur several weeks (or even months) after amiodarone treatment has been stopped.

Anaesthetics given during tri/tetracyclic antidepressant 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.

Dosulepin should not be given concurrently with an MAO inhibitor nor within 14 days of ceasing such treatment. Concomitant treatment of MAOIs, tramadol or selegiline with tricyclic antidepressants may cause CNS toxicity.

In general, drug interactions that cause the plasma concentration of dosulepin to increase may also increase the risk of side effects, especially cardiovascular and CNS toxicity.

Concomitant administration of dosulepin and selective serotonin re-uptake inhibitors (SSRIs) should be avoided. The plasma concentrations of tricyclic antidepressants are increased when taken with SSRI antidepressants, diltiazem, cimetidine, disulfiram, methylphenidate, ritonavir or verapamil.

The effects of tricyclic antidepressants may be antagonised by oestrogens. However the antidepressant side effects may be increased due to increased plasma concentrations. In the case of hormone replacement therapy, the low dose of oestrogens is unlikely to induce interactions.

Antagonism of the anticonvulsant effect of antiepileptics (such as carbamazepine, barbiturates and primidone) may occur with dosulepin, as well as increased metabolism of dosulepin leading to a reduced antidepressant effect.

When taken with rifampicin the plasma concentrations of dosulepin may be reduced and hence the antidepressant effect is reduced.
The manufacturers of apraclonidine and brimonidine advise to avoid concomitant use with tricyclic antidepressants. The manufacturer of entacapone advises caution with tricyclic antidepressants.

Dosulepin may alter the pharmacological effect of some concurrently administered drugs including CNS depressants such as alcohol and narcotic analgesics; the effect of these will be potentiated, as will be the effects of adrenaline and noradrenaline (some local anaesthetics contain these sympathomimetics). Side effects when taking nefopam with dosulepin may be increased.

There is an increased risk of postural hypotension when diuretics are taken with tricyclic antidepressants

The hypotensive activity of certain antihypertensive agents (e.g. betanidine, debrisoquine, guanethidine, clonidine and adrenergic neuron blockers) may be reduced by dosulepin. There is also the possibility of increased risk of hypotension on clonidine withdrawal. It would be advisable to review all antihypertensive therapy during treatment with tricyclic antidepressants.

The antimuscarinic side effects of antihistamines, phenothiazines and clozapine and the effect of antimuscarinic drugs may be increased during treatment with dosulepin.

Dosulepin taken with baclofen may give an enhanced muscle relaxant effect.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is no evidence as to the drug safety in human pregnancy nor is there evidence from animal work that it is free from hazard. Only use during pregnancy, especially during the first and last trimesters, if there are compelling reasons.

Breast-feeding
There is evidence that dosulepin is secreted in breast milk. Although this is at levels which are unlikely to cause problems, caution should be exercised when prescribing to breastfeeding women.

4.7 Effects on ability to drive and use machines

Initially, Dosulepin may impair alertness. In view of this and the possible side effects of drowsiness and confusion, patients should be warned of this possibility and if this occurs it is advisable not to drive or operating machinery.

4.8 Undesirable effects

The following adverse effects have been reported with tricyclic antidepressants, although not necessarily with dosulepin. Atropine-like side effects including dry mouth, disturbances of accommodation, tachycardia, constipation and hesitancy of micturition are common early in treatment, but usually lessen.

Withdrawal symptoms may occur on abrupt cessation of tricyclic therapy and include insomnia, irritability headache, nausea, giddiness, panic-anxiety, extreme motor
restlessness and excessive perspiration, therefore removal of therapy should be gradual (see section 4.4). 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 dosulepin.

**Blood and lymphatic system disorders:**
Rare: depression of bone marrow, agranulocytosis, eosinophilia and thrombocytopenia

**Immune system disorders:**
Hypersensitivity reactions

**Endocrine disorders:**
Inappropriate ADH secretion has been recorded.

**Metabolism and nutrition:**
Hyponatraemia

**Psychiatric disorders:**
Drowsiness, sleep disturbances and confusion (particularly in the elderly), nervousness
Rare: hypomania
Psychotic manifestations, including mania and paranoid delusions may be exacerbated during treatment with tricyclic antidepressants. Latent schizophrenia may be precipitated.

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

**Nervous system disorders:**
Taste disturbances, tremor, movement disorders, neuroleptic malignant syndrome, dyskinesias, convulsions

**Eye disorders:**
Common in early treatment: disturbances of accommodation

**Cardiac disorders:**
Common in early treatment: tachycardia
Cardiac arrhythmias and severe hypotension - likely to occur with high dosage or in deliberate overdosage, but may also occur in patients with pre-existing heart disease taking normal dosage or suffering from hyperthyroidism.

**Vascular disorders:**
Postural hypotension, occasional hypertension, dizziness, weakness and fatigue

**Gastrointestinal disorders:**
Common in early treatment: dry mouth, constipation
Other: Nausea, vomiting, gastric irritation

**Hepato-biliary disorders:**
Rare: hepatitis, cholestatic jaundice

**Skin and subcutaneous tissue disorders:**
Skin rashes, sweating

**Renal and urinary disorders:**
Common in early treatment: hesitancy of micturition.
Toxic levels may be reached in patients with severe renal problems.

**Reproductive system and breast disorders:**
Interference with sexual function may occur.

Incidents of galactorrhoea and gynaecomastia have been recorded.

**Investigations:**
Increased intraocular pressure, changes in blood sugar and weight loss may occur as may weight gain and the latter is sometimes associated with inappropriate appetite (carbohydrate craving).

Abnormal or altered liver function test results have been recorded with patients taking tricyclic antidepressants.

**General disorders:**
Speech difficulties, photosensitisation and idiosyncratic alveolitis which may prove fatal.

**Class effects:**
Epidemiological studies, mainly conducted in patients 50 year of age and older, show an increased risk of bone fracture in patients receiving SSRs and TCAs. The mechanism leading to this risk is unknown.

**Reporting of suspected adverse reactions**
Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard.

### 4.9 Overdose

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

All children ingesting dosulepin should be assessed by a physician.

Onset of toxicity occurs within 4-6 hours

**Symptoms**
The first signs of overdose appear up to two hours after the drug has been taken and take the form of severe anticholinergic reactions. Symptoms may include dry mouth, excitement, restlessness, ataxia, drowsiness, loss of consciousness, muscle twitching, widely dilated pupils, hyperreflexia, sinus tachycardia, hypothermia, visual hallucinations, delirium, urinary retention, paralytic ileus, and respiratory or metabolic alkalosis. In severe overdosage, convulsions, myoclonus, hypotension, respiratory and cardiac depression may develop with life threatening cardiac arrhythmias which may even occur after apparent recovery.

**Management**
- A clear airway and adequate ventilation should be ensured. Hypoxia and acid-base imbalances should be corrected by assisted ventilation and IV 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. The benefit of gastric lavage is uncertain and the technique should be avoided in any patient with an impaired airway.
- Blood pressure, pulse and cardiac rhythm should be monitored for at least 6hrs after ingestion.
Arrhythmias are best treated by correcting hypoxia and acid-base disturbances. Specialist poisons advice should be sought before using any antiarrhythmic agents as these may exacerbate the arrhythmia.

In cases of cardiac arrest, persist with prolonged CPR (for at least 1 hr).

Convulsions should be controlled with IV diazepam or lorazepam.

Bed rest is advisable, even after recovery.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Non-selective monoamine reuptake inhibitors

ATC Code: N06A A16

**Mechanism of action**
Dosulepin is a tricyclic antidepressant with similar actions to those of amitriptyline. It has marked anticholinergic and sedative properties, and prevents the re-uptake (and hence the inactivation) of noradrenaline and serotonin at nerve terminals. Its mode of action in depression is not fully understood. In addition, dosulepin inhibits the neuronal uptake of dopamine.

**Pharmacodynamic effects**
As a result of its effects on monoamine levels, dosulepin appears to produce adaptive changes in the brain by reducing or down-regulating both noradrenaline-induced cyclic-AMP formation and noradrenaline receptor numbers.

### 5.2 Pharmacokinetic properties

**Absorption**
Dosulepin is readily absorbed from the gastro-intestinal tract. Since dosulepin slows gastro-intestinal transit time absorption can, however, be delayed, particularly in overdosage.

**Biotransformation**
It is extensively demethylated by first-pass metabolism in the liver to its primary active metabolite, desmethyldosulepin (also termed northiaden). Paths of metabolism also include s-oxidation.

**Elimination**
Dosulepin is excreted in the urine, mainly in the form of its metabolites; appreciable amounts are also excreted in the faeces. Dosulepin is excreted in breast milk. The half-life for dosulepin and its metabolites is reported to be about 50 hours.

### 5.3 Preclinical safety data

Not applicable
6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Lactose monohydrate  
Maize starch  
Povidone  
Sodium starch glycollate  
Magnesium stearate

Coating:
Red colorant containing:  
Lactose  
Hypermellose  
Ponceau 4R Aluminium Lake (E124)  
Polyethylene glycol 4000  
Titanium Dioxide (E171)  
Yellow Iron Oxide (E172)  
Sunset Yellow FCF Aluminium Lake FD & C Yellow No. 6 (E110)

6.2 Incompatibilities

No other major incompatibilities are known

6.3 Shelf life

250μm opaque UPVC/Al: 2 years  
PVdC coated PVC/Al: 5 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Blister packs: UPVC/Child resistant push through foil blisters (250μm opaque UPVC/20μm Al with 15μm PVC film) in pack sizes of 14 or 28 tablets  
or PVdC coated PVC/Child resistant push through foil blisters (60g/m² PVdC on 250μm PVC/20μm Al with 15μm PVC film) in pack sizes of 14 or 28 tablets.
6.6 Special precautions for disposal
No special instructions

7 MARKETING AUTHORISATION HOLDER
Genethics Europe Limited
41 - 43 Klimentos
Klimentos Tower
Nicosia 1061
Cyprus

8 MARKETING AUTHORISATION NUMBER(S)
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