SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

DOSULEPIN TABLETS 75 MG

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Dosulepin Hydrochloride BP 75 mg

3 PHARMACEUTICAL FORM

Tablets

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

Dosulepin Tablets 75mg are for oral administration.

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 to 50 mg three times daily or, alternatively, 75 to 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.

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.

CHILDREN

Not recommended.

4.3 Contraindications

Recent Myocardial Infarction. Any degree of heart block of other cardiac arrhythmias. Mania. Severe Liver Disease.

4.4 Special warnings and precautions for use

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 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 which may increase the risk of toxicity associated with Dosulepin (See Section 4.5)
- Patients should be advised to store the tablets securely, out of sight and reach of children.
- In cases of overdose, patients should seek IMMEDIATE MEDICAL ATTENTION (see section 4.9)

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.

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).

Avoid if possible in patients with narrow angle glaucoma, symptoms suggestive of prostatic hypertrophy and a history of epilepsy.

Tricyclic antidepressants potentiate the central nervous depressant action of alcohol.

Anaesthetics given during tri/tetracyclic antidepressants 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.

Hyperthyroid patients may have cardiac arrhythmias with Dosulepin therapy.

Toxic blood levels may develop in severe renal cases.

Latent schizophrenia may be activated by Dosulepin.

Abrupt withdrawal may induce headache, nausea, insomnia, giddiness, panic anxiety and extreme motor restlessness.

4.5 Interaction with other medicinal products and other forms of interaction

Dosulepin should not be given concurrently with a MAO inhibitor nor within fourteen days of ceasing such treatment.

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 nonadrenaline (some local anaesthetics contain these sympathomimetics). The hypotensive activity of certain antihypertensive agents (e.g. bethanidine, debrisoquine, guanethidine) may be reduced by Dosulepin.

It would be advisable to review all anti-hypertensive therapy during treatment with tricyclic antidepressants.

Barbiturates may decrease and methyl phenidate may increase the serum concentration of Dosulepin and thus affect its antidepressant action.

4.6 Pregnancy and lactation

There is no evidence as to the safety of Dosulepin 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.

When administered during lactation, the results from a study in two patients indicated that Dosulepin is not actively secreted into the breast milk. Assuming a daily milk intake of 150 ml/kg (2½ oz/lb) on a weight basis (mg/kg) the baby would ingest 1/650 of the adult dose of the drug. Other factors to be taken into account include the range of maternal blood levels, the presence of metabolites and the lowered drug metabolising capacity of babies which may result in elevated serum levels of unchanged drug.

4.7 Effects on ability to drive and use machines

Dosulepin may impair alertness; patients likely to drive vehicles or operate machinery should be warned of this possibility.

4.8 Undesirable effects

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

Other adverse effects include drowsiness, sweating, postural hypotension, tremor and skin rashes. Interference with sexual function may occur. Serious adverse effects are rare. These include depression of the bone marrow, agranulocytosis, cholestatic jaundice, hypomania and convulsions.

Psychotic manifestations, including mania and paranoid delusions may be exacerbated during treatment with tricyclic antidepressants. Withdrawal symptoms may occur on abrupt cessation of tricyclic therapy and include insomnia, irritability and excessive perspiration. 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.

Cardiac arrhythmias and severe hypotension are likely to occur with high dosage or in deliberate overdosage. They may also occur in patients with pre-existing heart disease taking normal dosage.

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

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.

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.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Dosulepin is a tricyclic antidepressant with similar actions to amitriptyline.

5.2 Pharmacokinetic properties

Dosulepin is readily absorbed from the gastrointestinal tract and extensively metabolised in the liver, on first pass, to its primary metabolite desmethylDosulepin (also termed northiaden). Since Dosulepin slows intestinal transit time, absorption can, however be delayed particularly in overdosage.

Metabolic pathways include S-oxidation to Dosulepin and northiaden S-oxides. Dosulepin is excreted in the urine, mainly in the form of metabolites; small amounts are also excreted in the faeces. A half life of about 19 - 33 hours has been reported for Dosulepin and its metabolites.

Dosulepin is excreted in breast milk.

5.3 Preclinical safety data

There are no additional data of relevance to the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The tablets contain Lactose Monohydrate PhEur, Maize Starch PhEur, Povidone K29/32 PhEur, Talc PhEur, Sodium Starch Glycollate (Type A) PhEur and Magnesium Stearate PhEur. The coating contains polyvinyl alcohol, talc, lecithin soya, xanthan gum, carnauba wax PhEur, Ponceau 4R (E124) and titanium dioxide USP.

6.2 Incompatibilities

None known.

6.3 Shelf life

Three years.

6.4 Special precautions for storage

Store in a dry place below 25°C.

6.5 Nature and contents of container

PVC / foil blisters of 28 tablets.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Generics [UK] Limited
T/A Mylan
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Potters Bar
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EN6 1TL

8 MARKETING AUTHORISATION NUMBER(S)

PL 04569/0240

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