SUMMARY OF PRODUCT CHARACTERISTICS

1. TRADE NAME OF THE MEDICINAL PRODUCT

Dosulepin Tablets BP 75 mg.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 75 mg dosulepin hydrochloride.

Excipient(s) with known effect

Each dosage unit contains traces of Sucrose, Ponceau red, Sunset yellow and Benzoate salt.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets
Red sugar coated biconvex tablets, coded 'APS' or plain on one side and 75/1129 on the reverse.

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 in divided doses or as a single dose at night. The dose may be increased to two 75 mg tablets after a few days if required. In

certain circumstances e.g. under hospital conditions, dosages up to 225 mg daily have been used.

Paediatric population — The use of dosulepin is not recommended in children.

The Elderly — 50 - 75 mg daily initially (For the 50 mg dose, the 25 mg capsule is appropriate). 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.

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.

Method of administration
For oral administration.

4.3. Contra-indications

Dosulepin is contra-indicated in patients who have had a recent myocardial infarction or in patients with heart block of any degree or other cardiac arrhythmias. It is also contra-indicated in mania and in severe liver disease. Hypersensitivity to dosulepin or to any of the excipients.

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 tablets securely, out of sight and reach of children.

In cases of overdose, patients should seek IMMEDIATE MEDICAL ATTENTION (see section 4.9)

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 hydrochloride should be avoided in epileptic patients. 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).

Administration should be avoided if possible in patients with narrow angle glaucoma and 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.

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.

Conduction defects or cardiac arrhythmias may occur in hyperthyroid patients.

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

The elderly are particularly susceptible to experience adverse reactions to antidepressants. In particular they may suffer from agitation, confusion and postural hypotension.

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.

It is recommended that antidepressants are withdrawn gradually, as withdrawal reactions may occur (see 4.8).

Hyponatraemia (usually in the elderly and possibly due to inappropriate secretion of 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.

Serotonin syndrome
Concomitant administration of dosulepin and buprenorphine may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5).

If concomitant treatment with buprenorphine containing medicinal products is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

Excipients
The tablets contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

Benzoate salt
This medicine contains traces of benzoate salt in each dosage unit.

This medicine contains colours called sunset yellow and Ponceau red in traces which may cause allergic reactions.

4.5 Interactions with other Medicinal Products and other forms of Interaction

Dosulepin hydrochloride should not be administered concurrently with monoamine oxidase inhibitors nor within 14 days of cessation of such treatment.

Concomitant administration of dosulepin and selective serotonin re-uptake inhibitors (SSRIs) should be avoided. Increases in plasma tricyclic antidepressant levels have been reported with some SSRIs and dosulepin.

Dosulepin should be used cautiously when co-administered with buprenorphine/opioids as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

Dosulepin hydrochloride may potentiate the effects of alcohol and narcotic analgesics, also adrenaline and noradrenaline which are contained in some local anaesthetics. Anaesthetics given during tricyclic antidepressant therapy may increase the risk of arrhythmias and hypotension.

The hypotensive effect of some antihypertensive agents (e.g. debrisoquine, guanethidine) may be reduced by dosulepin hydrochloride. It is advisable to review all antihypertensive therapy if administered concurrently with tricyclic antidepressants.

Dosulepin has quinidine-like actions on the heart. Therefore, its concomitant use with other drugs which may affect cardiac conduction (e.g. sotalol, terfenadine, halofantrine) should be avoided.

Barbiturates may decrease and methylphenidate, phenothiazines and oral contraceptives may increase the serum concentration of dosulepin and thus affect its antidepressant action.

4.6. Pregnancy and Lactation

Pregnancy

There is inadequate evidence as to the safety of the drug during human pregnancy, therefore it should only be administered if considered essential.

Breast-feeding

There is evidence that dosulepin is secreted in breast milk but this is at levels which are unlikely to cause problems.

4.7. Effects on Ability to Drive and Use Machines

Dosulepin may cause drowsiness in some patients, if this occurs it is advisable not to drive or operate machinery.

4.8. Undesirable Effects

Adverse effects include drowsiness, sweating, postural or orthostatic hypotension, tremor, skin rashes, nervousness, insomnia, occasional hypertension, dizziness, weakness and fatigue, ataxia, epileptiform seizures, occasional extrapyramidal symptoms including speech difficulties, gastric irritation with nausea and vomiting, photosensitization and idiosyncratic alveolitis which may prove fatal.

Interference with sexual function may occur.

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

Other serious adverse effects are rare and include: bone marrow depression, eosinophilia, thrombocytopenia and agranulocytosis, Hepatitis (including altered liver function), cholestatic jaundice, hypomania, convulsions and inappropriate ADH secretion. Psychotic manifestations including mania and paranoid delusions may be exacerbated during treatment with tricyclic antidepressants.

Weight loss may occur as may weight gain and the latter is sometimes associated with inappropriate appetite (carbohydrate craving).
Withdrawal symptoms may occur if treatment is ceased abruptly, these include insomnia, irritability, headache, nausea, giddiness, panic-anxiety, extreme motor restlessness and excessive perspiration (see 4.4). Similar symptoms have been

reported in neonates whose mothers received tricyclic antidepressants during the third trimester.

In high dosage or in deliberate overdosage, cardiac arrhythmias and severe hypotension are likely to occur. These effects 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).

Class effects
Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving tricyclic antidepressants. 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 or search for MHRA Yellow Card in the Google Play or Apple App Store.

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.

Signs of overdosage are dryness of the mouth, ataxia, drowsiness, loss of consciousness, muscle twitching, widely dilated pupils, hyperreflexia, sinus tachycardia, hypothermia, visual hallucinations, delirium, urinary retention, paralytic ileus, excitement, restlessness 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 1hr).
- Convulsions should be controlled with iv diazepam or lorazepam.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

ATC Code: NO6A A16 (Non-selective monoamine reuptake inhibitors)

Dosulepin is a tricycle antidepressant with similar actions to those of amitriptyline. It prevents the re-uptake (and hence the inactivation) of noradrenaline and serotonin at nerve terminals. The mode of action in the treatment of depression is not fully understood. In addition, dosulepin inhibits the neuronal uptake of dopamine.

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

Dosulepin is readily absorbed from the gastrointestinal tract. The half life for dosulepin and its metabolites is reported to be about 50 hours. It is metabolised in the liver to its primary active metabolite, desmethyldosulepin. It is excreted in the urine, mainly in the form of metabolites. Some is also excreted in the faeces. Dosulepin has been found in breast milk.

5.3. Preclinical Safety Data

Pre-clinical information has not been included because the safety profile of dosulepin has been established after many years of clinical use. Please refer to Section 4.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

The tablet contains:
Calcium Phosphate
Maize Starch
Povidone
Sodium Carboxymethylcellulose
Magnesium Stearate (E572)
Hydrolysed gelatin
Sucrose

Talc (E553)

The coating contains:
Sucrose
Shellac
Carnauba wax
Beeswax
Sodium benzoate
Titanium dioxide (E171)
Ponceau red (E124)
Sunset yellow (E110)
Indigotine (E132)

The printing ink contains:
Shellac
Black iron oxide (E172)
Propylene Glycol (E1520).

6.2. Incompatibilities

Not applicable.

6.3. Shelf Life

2 years.

6.4 Special Precautions for Storage

Store in a dry place at or below 25°C. Protect from light.

6.5. Nature and Contents of Container

Child resistant blister strips (PVC/PVdC/Glassine/aluminium foil) in packs of 14 and 28 tablets.

Not all pack sizes may be marketed

6.6. Instruction for Use/Handling

Not applicable.

7. MARKETING AUTHORISATION HOLDER

TEVA UK Limited,

Brampton Road, Hampden Park,
Eastbourne, East Sussex, BN22 9AG

8. MARKETING AUTHORISATION NUMBER

PL 00289/0108

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

05/02/97

10. DATE OF (PARTIAL) REVISION OF THE TEXT

10/03/2021

POM