SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Doxepin 50 mg Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 50 mg of doxepin (as doxepin hydrochloride)
Excipient(s) with known effect:
Each hard capsule contains 263.88 mg lactose monohydrate.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard Capsule
Opaque hard gelatin, light blue capsules (size 1).

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptoms of depressive illness in adults, especially where sedation is required.

4.2 Posology and method of administration

Posology

The optimum oral dose depends on the severity of the condition and the individual patient's response. The dose required may vary from 25-300mg daily. Doses up to 100mg daily may be given on a divided or once daily schedule. Should doses over 100mg daily be required, they should be administered in three divided doses daily. 100mg is the maximum dose recommended at any one time. This dose may be given at bedtime.
For the majority of patients with moderate or severe symptoms, it is recommended that treatment commences with an initial dose of 75mg daily. Many of these patients will respond satisfactorily at this dose level. For patients who do not, the dosage may be adjusted according to individual response. In more severely ill patients, it may be necessary to administer a dose of up to 300mg in divided doses daily, to obtain a clinical response.
In patients where insomnia is a troublesome symptom, it is recommended that the total daily dose be divided so that a higher proportion is given for the evening dose; similarly, if drowsiness is experienced as a side effect of treatment, Doxepin Capsules may be administered by this regimen or the

dosage may be reduced. It is often possible, having once obtained a satisfactory therapeutic response, to reduce the dose for maintenance therapy. The optimal anti-depressant effect may not be evident for two to three weeks.
Paediatric population
The safety and efficacy of doxepin in children under 18 years have not been established.
Elderly
In general, dose selection for an elderly patient should be cautious, starting at the low end of the dosing range, reflecting the greater susceptibility of elderly people to typical side effects of the drug.
Hepatic impairment
Dosage reduction may be required in patients with hepatic impairment (see 'Special warnings and special precautions for use').
Renal impairment
Dosage reduction may be required in patients with renal impairment (see 'Special warnings and special precautions for use').
Method of administration
For oral use. Capsules should be swallowed whole with fluid.

4.3 Contraindications

Doxepin is contra-indicated in individuals who have shown hypersensitivity to tricyclic antidepressants (TCAs), doxepin, or any of the inactive ingredients. Doxepin is also contra-indicated in patients with mania, severe liver disease, lactation, glaucoma, tendency to urinary retention.

4.4 Special warnings and precautions for use

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 with 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.
The once-a-day dosage regimen of Doxepin Capsules in patients with intercurrent illness or patients taking other medications should be carefully

adjusted. This is especially important in patients receiving other medications with anti-cholinergic effects.
The use of Doxepin Capsules on a once-a-day dosage regimen in geriatric patients should be adjusted carefully on the basis of the patient's condition.
The elderly are particularly liable to experience toxic effects, especially agitation, confusion and postural hypotension. The initial dose should be increased with caution under close supervision. Half the normal maintenance dose may be sufficient to produce a satisfactory clinical response.
Patients should be warned that drowsiness may occur with the use of Doxepin Capsules. Patients should also be cautioned that their response to alcohol may be potentiated.
Caution should be observed in the treatment of patients with severe cardiovascular disease, including patients with heart block, cardiac arrhythmia and those who have experienced a recent myocardial infarction.
Use in hepatic/renal impairment Use with caution in patients with hepatic and/or renal impairment.
Use in patients with epilepsy Use with caution in patients with a history of epilepsy.
Since suicide is an inherent risk in any depressed patient until significant improvement has occurred, patients should be closely supervised during early therapy.
Patients with benign prostatic hyperplasia may experience an increase in associated urinary retention (see 'Undesirable effects').
Doxepin 50 mg Hard Capsules contain sodium.
This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially "sodium-free".
Information relates to a threshold based on the total amount of sodium in the medicinal product. It is especially relevant to products used in patients on a low sodium diet, to provide information to prescribers and reassurance to patients concerning the low level of sodium in the product.
Doxepin 50 mg Hard Capsules contain lactose monohydrate.
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Doxepin, like other tricyclic antidepressants (TCAs), is metabolised by cytochrome P450 (CYP) 2D6. Inhibitors or substrates of CYP2D6 (e.g. quinidine, selective serotonin reuptake inhibitors [SSRIs]) may increase the plasma concentration of TCAs when administered concomitantly. The extent of interaction depends on the variability of effect on CYP2D6 and the therapeutic index of the TCA. The clinical significance of this interaction with doxepin has not been systematically evaluated.
Combined use with other anti-depressants, alcohol or anti-anxiety agents should be undertaken with due recognition of the possibility of potentiation. It is known, for example, that monoamine oxidase inhibitors may potentiate other drug effects, therefore Doxepin Capsules should not be given concurrently, or within two weeks of cessation of therapy, with monoamine oxidase inhibitors.

Cimetidine has been reported to produce clinically significant fluctuations in steady-state serum concentrations of doxepin.
Doxepin should not be given with sympathomimetic agents such as ephedrine, isoprenaline, noradrenaline, phenylephrine and phenylpropanolamine.
General anaesthetics and local anaesthetics (containing sympathomimetics) given during tricyclic or tetracyclic anti-depressant therapy may increase the risk of arrhythmias and hypotension, or hypertension. If surgery is necessary, the anaesthetist should be informed that a patient is being so treated.
Doxepin may decrease the anti-hypertensive effect of agents such as debrisoquine, bethanidine, guanethidine and possibly clonidine. It usually requires daily doses of doxepin in excess of 150mg before any effect on the action of guanethidine is seen. It would be advisable to review all antihypertensive therapy during treatment with tricyclic anti-depressants.
Barbiturates may increase the rate of metabolism of doxepin.
Doxepin Capsules may reduce the effect of sublingual nitrates owing to dry mouth.
The dose of thyroid hormone medication may need reducing if Doxepin Capsules are being given concurrently.

4.6 Fertility, pregnancy and lactation

Pregnancy

Doxepin crosses the placenta. Reproduction studies have been performed in rats, rabbits and monkeys and there was no evidence of harm to the animal foetus. The relevance to humans is not known. Since there is insufficient experience in pregnant women who have received this drug, its safety in pregnancy has not been established.

Breast-feeding

Doxepin and its active metabolite desmethyldoxepin are excreted in breast milk. There has been a report of apnoea and drowsiness occurring in a nursing infant whose mother was taking doxepin. The use of Doxepin Capsules is contraindicated during lactation.

Fertility

There are no fertility data available.

4.7 Effects on ability to drive and use machines

Since drowsiness may occur with the use of Doxepin Capsules, patients should be warned of the possibility and cautioned against driving a car or operating machinery while taking this drug.

4.8 Undesirable effects

Doxepin Capsules are well tolerated. Most side-effects are mild and generally disappear with continued treatment, or if necessary a reduction in dose.
Note: Some of the side-effects noted below have not been specifically reported with Doxepin Capsules. However, due to the close pharmacological similarities amongst the tricyclics, the reactions should be considered when prescribing Doxepin Capsules.

The most common side-effects to Doxepin Capsules are drowsiness, dry mouth and constipation. For further details see below under central nervous system and anti-cholinergic effects.

***Suicidal Ideation and Behaviours*:** Cases of suicidal ideation and suicidal behaviours have been reported during doxepin therapy or early after treatment discontinuation (see section 4.4).

Bone fractures: 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.

Anti-cholinergic effects: Anti-cholinergic effects are relatively common and may occur immediately following the first dose of a tricyclic anti-depressant. Dry mouth and constipation are the most common anti-cholinergic effects. Blurred vision and sweating occur occasionally. Urinary retention is rare except in predisposed males who have an enlarged prostate gland. Tolerance is often achieved if treatment is continued. If these undesirable effects do not subside with continued therapy, or if they become severe, it may be necessary to reduce the dosage.

Central nervous system effects: Drowsiness is the most commonly noticed side effect. This tends to disappear as therapy is continued. Insomnia and nightmares have also been reported. Other infrequently reported CNS side effects are confusion, disorientation, agitation, numbness or paraesthesiae, tremor (which is usually mild). But at high doses, in susceptible individuals (particularly the elderly) other extrapyramidal symptoms may occur including tardive dyskinesia. Rarely reported are hallucinations, ataxia (generally where mixtures of CNS drugs have been given), and convulsions. Convulsions are unlikely except in people predisposed to seizure activity by brain damage or alcohol and drug abuse.

Psychotic manifestations, including mania and paranoid delusions may be exacerbated during treatment with tricyclic anti-depressants.

Cardiovascular: Cardiovascular effects including postural hypotension, and tachycardia have been reported occasionally and changes in ECG parameters (widening of the QRS and PR interval) very rarely (see ‘Special warnings and special precautions for use’).

Allergic: Allergic reactions to tricyclic anti-depressants are uncommon. They include skin rash, facial oedema, photosensitisation, pruritus and urticaria.

Haematological: Rare cases of eosinophilia and bone marrow depression manifesting as agranulocytosis, leucopenia, thrombocytopenia and purpura. Haemolytic anaemia.

Gastro-intestinal: Nausea, vomiting, indigestion, taste disturbances, diarrhoea, anorexia and aphthous stomatitis have been reported (see ‘Anti-cholinergic effects’).

Endocrine: Occasional reports of raised or lowered libido, testicular swelling, raised or lowered blood sugar levels. Rarely the syndrome of inappropriate anti-diuretic hormone secretion, gynaecomastia, enlargement of breasts and galactorrhoea in the female.

Other: Dizziness, weight gain, chills, fatigue, weakness, flushing, alopecia, headache, exacerbation of asthma and hyperpyrexia (in association with chlorpromazine) have been occasionally observed. Rare reports of jaundice and of tinnitus.

Withdrawal: Withdrawal symptoms may occur on abrupt cessation of tricyclic anti-depressant therapy and include insomnia, irritability and excessive perspiration. Withdrawal symptoms in neonates whose mothers received tricyclic anti-depressants during the third trimester have also been reported and include respiratory depression, convulsions and "jitteriness" (hyperreflexia).

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 Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Signs and symptoms

Mild: drowsiness, stupor, blurred vision, excessive dryness of mouth.
Severe: respiratory depression, hypotension, coma, convulsions, cardiac arrhythmias and tachycardias.
Also urinary retention (bladder atony), decreased gastrointestinal motility (paralytic ileus), hyperthermia (or hypothermia), hypertension, dilated pupils, hyperactive reflexes.
Deaths have been reported involving overdoses of doxepin. The reported cases involved doxepin alone and in combination with other drugs and/or alcohol.

Management and treatment

Mild: observation and supportive therapy is all that is usually necessary.
Severe: medical management of severe doxepin overdosage consists of aggressive supportive therapy. If the patient is conscious, gastric lavage with appropriate precautions to prevent pulmonary aspiration should be performed even though doxepin is rapidly absorbed. The use of activated charcoal has been recommended, as has been continuous gastric lavage with saline for 24 hours or more. An adequate airway should be established in comatose patients and assisted ventilation used if necessary. ECG monitoring may be required for several days, since relapse after apparent recovery has been reported. Arrhythmias should be treated with the appropriate anti-arrhythmic agent. It has been reported that many of the cardiovascular and CNS symptoms of tricyclic anti-depressant poisoning in adults may be reversed by the slow intravenous administration of 1mg to 3mg of physostigmine salicylate. Because physostigmine is rapidly metabolised, the dosage should be repeated as required. Convulsions may respond to standard anti-convulsant therapy. However, barbiturates may potentiate any respiratory depression. Dialysis and forced diuresis generally are not of value in the management of overdosage due to high tissue and protein binding of doxepin.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidepressants, Non-selective monoamine reuptake inhibitors, ATC code: N06AA12
The mechanism of action of doxepin is not definitely known. It is not a central nervous system stimulant nor a monoamine oxidase inhibitor. The current hypothesis is that the clinical effects are due, at least in part, to influences on the adrenergic activity at the synapses so that deactivation of noradrenaline by reuptake into the nerve terminals is prevented. In animal studies anticholinergic, anti-serotonergic and anti-histaminergic effects on smooth muscle have been demonstrated. At higher than usual clinical doses, adrenaline response was potentiated in animals. This effect was not demonstrated in humans.

5.2 Pharmacokinetic properties

Doxepin is well absorbed from the gastro-intestinal tract. Approximately 55%-87% of orally administered doxepin undergoes first pass metabolism in the liver, forming the primary active metabolite desmethyldoxepin.
In healthy volunteers, a single oral dose of 75mg resulted in peak plasma concentrations for doxepin ranging from 8.8-45.8 ng/ml (mean 26.1 ng/ml). Peak levels were reached between 2 and 4 hours (mean 2.9 hours) after administration. Peak levels for the primary metabolite desmethyldoxepin ranged from 4.8-14.5 ng/ml (mean 9.7 ng/ml) and were achieved between 2 and 10 hours after administration. The mean apparent volume of distribution for doxepin is approximately 20 l/kg. The protein binding for doxepin is approximately 76%. In healthy volunteers the plasma elimination half-life of doxepin ranged from 8 to 24 hours (mean 17 hours). The half-life of desmethyldoxepin ranged from 33-80 hours (mean 51 hours). Mean plasma clearance for doxepin is approximately 0.84 l/kg.hr. Paths of metabolism of doxepin include demethylation, N-oxidation, hydroxylation and glucuronide formation. Doxepin is excreted primarily in the urine, mainly as its metabolites, either free or in conjugate form.

5.3 Preclinical safety data

Doxepin is a drug on which extensive clinical experience has been obtained. There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Lactose monohydrate
Sodium lauryl sulphate (E487)
Magnesium stearate (E572)
Shell Formulation

Indigotine – FD&C Blue 2 (Including sodium.) (E132)
Titanium dioxide (E171)
Gelatin

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Doxepin 50 mg Hard Capsules are packed in PVC/PVDC/aluminium blisters.
Each blister contains 14 capsules.
Pack size: 28 hard capsules.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 49578/0009

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