

## **SUMMARY OF PRODUCT CHARACTERISTICS**

### **1 NAME OF THE MEDICINAL PRODUCT**

SINEPIN 50mg Capsules  
Doxepin 50mg Capsules

### **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Active Ingredient: Doxepin Hydrochloride BP  
The capsules contain Doxepin Hydrochloride BP equivalent to 50mg doxepin.

Excipient(s) with known effect

Each capsule also contains 200.00 mg of lactose.  
For the full list of excipients, see section 6.1.

### **3 PHARMACEUTICAL FORM**

Capsules  
Dark blue cap and blue body, opaque, size 2 hard gelatin capsules.

### **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 50mg 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 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**

Oral administration

### **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 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 50mg 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 50mg 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 50mg Capsules. Patients should also be cautioned that their response to alcohol may be potentiated.

Although Doxepin 50mg Capsules carry less risk than other tricyclic antidepressants, 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.

### ***Serotonin syndrome***

Concomitant administration of Doxepin 50mg Capsules and buprenorphine/opioids may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5).

If concomitant treatment of buprenorphine/ opioids 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.

***Hepatic/renal impairment***

Use with caution in patients with hepatic and/or renal impairment.

***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 50mg Capsule contains lactose***

Patients with rare hereditary problems of fructose intolerance, galactose intolerance, galactosaemia 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 50mg 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.

Sinepin 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 anti-hypertensive therapy during treatment with tricyclic anti-depressants.

Barbiturates may increase the rate of metabolism of doxepin.

Doxepin 50mg Capsules may reduce the effect of sublingual nitrates owing to dry mouth.

The dose of thyroid hormone medication may need reducing if Doxepin 50mg Capsules are being given concurrently.

Doxepin 50mg Capsules 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).

#### **4.6 Fertility, pregnancy and lactation**

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 50mg Capsules is contraindicated during lactation.

#### **4.7 Effects on ability to drive and use machines**

Since drowsiness may occur with the use of Doxepin 50mg 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**

Frequency is defined as: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), very rare ( $< 1/10,000$ ) and not known (cannot be estimated from the available data).

##### ***Note***

Some of the side-effects noted below have not been specifically reported with Doxepin 50mg Capsules. However, due to the close pharmacological similarities amongst the tricyclics, the reactions should be considered when prescribing Doxepin 50mg Capsules.

<b>System Organ Class</b>	<b>Adverse Reaction</b>	<b>Frequency</b>
<b>Blood and lymphatic system disorders</b>	Eosinophilia, agranulocytosis, leucopenia, thrombocytopenia, purpura, haemolytic anaemia	Rare
<b>Endocrine disorders</b>	Inappropriate anti-diuretic hormone secretion, gynaecomastia	Rare
<b>Metabolism and nutrition disorders</b>	Appetite decreased	Not known
<b>Psychiatric disorders</b>	Hallucinations	Rare
	Insomnia, nightmares, mania, paranoid delusions, confusion, disorientation, agitation, suicidal ideation, suicidal behaviour	Not known
<b>Renal and urinary disorders</b>	Urinary retention	Rare
<b>Reproductive system and breast disorders</b>	Breast enlargement, galactorrhoea	Rare
	Testicular swelling, libido increased or decreased	Not known
<b>Nervous system disorders</b>	Drowsiness	Common
	Ataxia, convulsions	Rare
	Tardive dyskinesia, dizziness, headache, dysgeusia, numbness, paraesthesia, tremor	Not known
<b>Ear and labyrinth disorders</b>	Tinnitus	Rare
<b>Eye disorders</b>	Blurred vision	Not known
<b>Cardiac disorders</b>	Tachycardia	Not known
<b>Gastrointestinal disorders</b>	Dry mouth, constipation	Common
	Nausea, vomiting, indigestion, diarrhoea	Not known
	Aphthous ulcer	Not known
<b>Hepatobiliary disorders</b>	Jaundice	Rare
<b>Investigations</b>	Electrocardiogram QRS complex prolonged, Electrocardiogram PR	Rare

	prolongation	
	Blood sugar increased, blood sugar decreased, Weight increased	Not known
<b>Respiratory, thoracic and mediastinal conditions</b>	Asthma	Not known
<b>Skin and subcutaneous tissue disorders</b>	Skin rash, facial oedema, photosensitivity, pruritus, urticaria	Uncommon
	Alopecia	Not known
<b>Musculoskeletal and connective tissue disorders</b>	Bone Fracture	Not known
<b>Vascular disorders</b>	Postural hypotension, flushing	Not known
<b>General disorders and administration site conditions</b>	Chills, fatigue, asthenia, hyperpyrexia, hyperhidrosis	Not known

#### 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](http://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

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 anti-cholinergic, 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 gastrointestinal 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**

There is no information relating to preclinical safety for doxepin.

### **6.1 List of excipients**

*Doxepin 50mg Capsule:* lactose, magnesium stearate, maize starch dried, sodium lauryl sulphate; capsule shell constituents: erythrosine (E127), gelatin, patent blue V (E131) and titanium dioxide (E171).

Doxepin 50mg Capsules are free of gluten and sucrose.

### **6.2 Incompatibilities**

None known

### **6.3 Shelf life**

3 years.

### **6.4 Special precautions for storage**

Store below 25°C.

### **6.5 Nature and contents of container**

Doxepin 50mg Capsules are available as:  
Packs of 28 capsules. Aluminium/PVC blister strips; 2 rows of 7 capsules per strip, 2 strips in a carton box.

### **6.6 Special precautions for disposal**

No special requirements.

## **7 MARKETING AUTHORISATION HOLDER**

Marlborough Pharmaceuticals Ltd  
Sovereign House, Miles Gray Road,  
Basildon, Essex SS14 3FR, UK

## **8 MARKETING AUTHORISATION NUMBER(S)**

PL 23138/0003

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

September 15<sup>th</sup> 2006

**10 DATE OF REVISION OF THE TEXT**

16/06/2021