Preparations

BP 2008: Dosulepin Capsules; Dosulepin Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Dothep; Prothiaden; ***Belg.:*** Prothiaden; ***Cz.:*** Prothiaden; ***Denm.:*** Prothiaden; ***Fr.:*** Prothiaden; ***Ger.:*** Idom; ***Hong Kong:*** Prothiaden; ***India:*** Prothiaden; ***Irl.:*** Dothep; Prothiaden; ***Ital.:*** Protiaden; ***Malaysia:*** Dothep; Prothiaden; ***Neth.:*** Prothiaden; ***NZ:*** Dopress; Prothiaden; ***Philipp.:*** Prothiaden; ***Port.:*** Protiadene; ***S.Afr.:*** Prothiaden; Thaden; ***Singapore:*** Espin; Prothiaden; ***Spain:*** Prothiaden; ***Switz.:*** Protiaden†; ***Thai.:*** Dopin†; Prothiaden†; ***UK:*** Dothapax†; Prepadine; Prothiaden.

Multi-ingredient: ***Austria:*** Harmomed.

Doxepin Hydrochloride

(BANM, USAN, rINNM)

Doksepiinihydrokloridi; Doksepin Hidroklorür; Doksepino hidrochloridas; Doksepiny chlorowodorek; Doxépine, chlorhydrate de; Doxepin-hidroklorid; Doxepin-hydrochlorid; Doxepinhydroklorid; Doxepini hydrochloridum; Hidrocloruro de doxepina; NSC-108160; P-3693A. (*E*)-3-(Dibenz[*b*,*e*]oxepin-11-ylidene) propyldimethylamine hydrochloride.

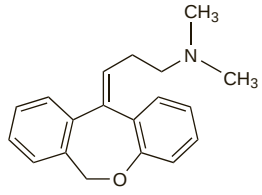
Доксепина Гидрохлорид

$C_{19}H_{21}NO,HCl$ = 315.8.

CAS — 1668-19-5 (doxepin); 1229-29-4 (doxepin hydrochloride); 4698-39-9 (doxepin hydrochloride, E-isomer); 25127-31-5 (doxepin hydrochloride, Z-isomer).

ATC — N06AA12.

ATC Vet — QN06AA12.



(doxepin)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*
Ph. Eur. 6.2 (Doxepin Hydrochloride). A white or almost white crystalline powder. Freely soluble in water, in alcohol, and in dichloromethane. Protect from light.
USP 31 (Doxepin Hydrochloride). It consists of a mixture of *Z*- and *E*-isomers.

Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p.376). Drowsiness and other systemic effects can also occur after topical application. In addition, local effects, most commonly burning and stinging, have been reported.

Breast feeding. For comments on the use of tricyclic antidepressants in breast feeding patients, see under Precautions for Amitriptyline, p.378.

Effects on the skin. Up to January 2002 the FDA was aware of 26 cases of allergic contact dermatitis associated with the use of doxepin 5% cream;[1] manifestations included eczema, urticaria, purpura, and papulovesicular lesions. Of the 20 cases where details were known, 13 occurred after use for more than the recommended 8 days. Patch testing was positive in the 21 cases where it was performed, supporting an allergic reaction rather than an exacerbation of the original condition.

1. Bonnel RA, *et al.* Allergic contact dermatitis from topical doxepin: Food and Drug Administration's postmarketing surveillance experience. *J Am Acad Dermatol* 2003; **48:** 294–6.

Overdosage. An infant became difficult to arouse after the application of doxepin cream 5% to about 50% of her body-surface; an entire 30-g tube of the cream was used in only 2 applications.[1] The cream is not recommended for use in children.

1. Zell-Kanter M, *et al.* Doxepin toxicity in a child following topical application. *Ann Pharmacother* 2000; **34:** 328–9.

Interactions

For interactions associated with tricyclic antidepressants, see Amitriptyline, p.379.

Pharmacokinetics

Doxepin is readily absorbed from the gastrointestinal tract after oral doses, and is extensively demethylated by first-pass metabolism in the liver, to its primary active metabolite, desmethyldoxepin. Doxepin is also absorbed through the skin after topical application.

Paths of metabolism of both doxepin and desmethyldoxepin include hydroxylation and *N*-oxidation. Doxepin is excreted in the urine, mainly in the form of its metabolites, either free or in conjugated form.

Doxepin and desmethyldoxepin are widely distributed throughout the body; the plasma protein binding of doxepin is about 76%. Doxepin has been estimated to have a plasma elimination half-life ranging from 8 to 24 hours, which may be considerably extended in overdosage; that of desmethyldoxepin is longer.

Doxepin crosses the blood-brain barrier and the placenta. It is distributed into breast milk (see Breast Feeding under Precautions in Amitriptyline, p.378).

◊ References.

1. Faulkner RD, *et al.* Multiple-dose doxepin kinetics in depressed patients. *Clin Pharmacol Ther* 1983; **34:** 509–15.
2. Joyce PR, Sharman JR. Doxepin plasma concentrations in clinical practice: could there be a pharmacokinetic explanation for low concentrations? *Clin Pharmacokinet* 1985; **10:** 365–70.

Uses and Administration

Doxepin is a dibenzoxepine tricyclic antidepressant with actions and uses similar to those of amitriptyline (p.381). It has moderate antimuscarinic and marked sedative properties and has serotonin reuptake inhibitor activity.

In the treatment of depression doxepin is given orally as the hydrochloride although doses are expressed in terms of the base; doxepin hydrochloride 84.8 mg is equivalent to about 75 mg of doxepin. The initial dose is 75 mg daily, gradually adjusted according to response. Doses of up to 300 mg daily may be required in severely depressed patients; mildly affected patients may respond to as little as 25 to 50 mg daily. Daily doses up to 100 mg may be given in divided doses or as a single dose at bedtime. If the total daily dose exceeds 100 mg, it should be given in 3 divided doses, although the largest portion, up to a maximum of 100 mg, may be given at bedtime. In the USA, the maximum single dose is 150 mg. A suggested starting dose in the elderly is 10 to 50 mg daily.

Doxepin hydrochloride has also been given by intramuscular or intravenous injection.

Doxepin should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Doxepin has histamine H_1- and H_2-antagonist activity and is used topically in a cream containing 5% of the hydrochloride for the short-term (up to 8 days) relief of moderate pruritus associated with various types of dermatitis (see below).

Headache. Tricyclic antidepressants can be effective in the management of some types of headache—see p.381.

References to the use of doxepin.

1. Wörz R, Scherhag R. Treatment of chronic tension headache with doxepin or amitriptyline—results of a double-blind study. *Headache Q* 1990; **1:** 216–23.

Insomnia. Doxepin is under investigation in the management of insomnia (p.957). Low oral doses of 1 to 6 mg at night are being studied.[1]

1. Roth T, *et al.* Efficacy and safety of doxepin 1 mg, 3 mg, and 6 mg in adults with primary insomnia. *Sleep* 2007; **30:** 1555–61.

Skin disorders. Tricyclic antidepressants have a wide range of pharmacological activity and some drugs in this group have notable antihistaminic actions. Doxepin in particular has very potent antihistaminic activity. It has been shown to be an effective oral alternative to conventional antihistamines in the treatment of chronic urticaria,[1-3] and to be an effective oral treatment for idiopathic cold urticaria.[4,5] In the case of cold urticaria doxepin may act by inhibiting release of a platelet-activating factor-like lipid.[5]

For an overview of the possible treatments for the various urticarias, including mention of the use of doxepin, see p.1584.

Like standard antihistamines (p.565) doxepin has also been used topically for the relief of pruritus (see also p.1582) associated with various types of allergic and inflammatory skin disorders[6,7] although some authorities remain to be convinced of its efficacy.[8,9] Topical application of doxepin can also produce contact dermatitis (see Effects on the Skin, above) and drowsiness and other systemic effects.

1. Greene SL, *et al.* Double-blind crossover study comparing doxepin with diphenhydramine for the treatment of chronic urticaria. *J Am Acad Dermatol* 1985; **12:** 669–75.
2. Harto A, *et al.* Doxepin in the treatment of chronic urticaria. *Dermatologica* 1985; **170:** 90–3.
3. Goldsobel AB, *et al.* Efficacy of doxepin in the treatment of chronic idiopathic urticaria. *J Allergy Clin Immunol* 1986; **78:** 867–73.
4. Neittaanmäki H, *et al.* Comparison of cinnarizine, cyproheptadine, doxepin, and hydroxyzine in treatment of idiopathic cold urticaria: usefulness of doxepin. *J Am Acad Dermatol* 1984; **11:** 483–9.
5. Grandel KE, *et al.* Association of platelet-activating factor with primary acquired cold urticaria. *N Engl J Med* 1985; **313:** 405–9.
6. Drake LA, *et al.* Relief of pruritus in patients with atopic dermatitis after treatment with topical doxepin cream. *J Am Acad Dermatol* 1994; **31:** 613–16.
7. Smith PF, Corelli RL. Doxepin in the management of pruritus associated with allergic cutaneous reactions. *Ann Pharmacother* 1997; **31:** 633–5.
8. Anonymous. Doxepin cream for pruritus. *Med Lett Drugs Ther* 1994; **36:** 99–100.
9. Anonymous. Doxepin cream for eczema? *Drug Ther Bull* 2000; **38:** 31–2.

Preparations

BP 2008: Doxepin Capsules;
USP 31: Doxepin Hydrochloride Capsules; Doxepin Hydrochloride Oral Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Doxederm†; ***Austral.:*** Deptran; Sinequan; ***Austria:*** Sinequan; ***Belg.:*** Sinequan; ***Canad.:*** Sinequan; Zonalon†; ***Denm.:*** Sinequan; ***Fin.:*** Doxal; ***Fr.:*** Quitaxon; ***Ger.:*** Aponal; Doneurin; Doxe; Doxepia; espadox†; Mareen; Sinquan†; ***Gr.:*** Sinequan; ***Hong Kong:*** Qualiquan; Sinequan; ***India:*** Spectra; ***Indon.:*** Sagalon; ***Irl.:*** Sinequan; Xepin†; ***Israel:*** Gilex; ***Mex.:*** Sinequan; ***Neth.:*** Sinequan; ***Norw.:*** Sinequan; ***NZ:*** Anten; ***Pol.:*** Sinequan; ***Spain:*** Sinequan; ***Switz.:*** Sinquane; ***Thai.:*** Sinequan; ***UK:*** Sinepin; Sinequan†; Xepin; ***USA:*** Prudoxin; Sinequan; Zonalon.

Duloxetine Hydrochloride

(BANM, USAN, rINNM)

Duloxétine, Chlorhydrate de; Duloxetini Hydrochloridum; Hidrocloruro de duloxetina; LY-248686 (duloxetine). (+)-(*S*)-*N*-Methyl-γ-(1-naphthyloxy)-2-thiophenepropylamine hydrochloride.

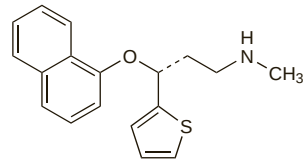
Дулоксетина Гидрохлорид

$C_{18}H_{19}NOS,HCl$ = 333.9.

CAS — 116539-59-4 (duloxetine); 136434-34-9 (duloxetine hydrochloride).

ATC — N06AX21.

ATC Vet — QN06AX21.



(duloxetine)

Adverse Effects and Treatment

Adverse effects reported most frequently with duloxetine include nausea, headache, insomnia, fatigue, somnolence, dry mouth, dizziness, and constipation. Other common adverse effects include anorexia, diarrhoea, dyspepsia, vomiting, anxiety, visual disturbances, tremor, weight gain or loss, sexual dysfunction, nervousness, lethargy, yawning, hot flushes, increased sweating, and pruritus. Dose-related increases in blood pressure have also been observed in some patients. Reports of reversible increases in liver enzymes, tachycardia, ecchymosis, urinary hesitation, skin rashes, and photosensitivity reactions are less common, and hepatitis, cholestatic jaundice, convulsions and activation of mania or hypomania have occurred rarely. Cases of orthostatic hypotension and syncope, serotonin syndrome, and akathisia have also been reported. Suicidal ideation may occur in some patients.

Hyponatraemia, possibly due to inappropriate secretion of antidiuretic hormone, has been associated with the use of antidepressants, particularly in the elderly.

In the treatment of overdosage oral activated charcoal should be considered if more than 7.5 mg/kg of duloxetine has been ingested and the patient presents within 1 hour of ingestion; this should be followed by