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.

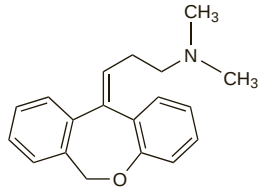
Доксепина Гидрохлорид

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

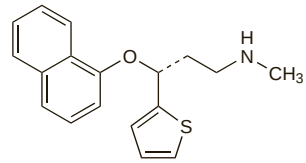
Дулоксетина Гидрохлорид

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

symptomatic and supportive therapy. Dialysis, haemoperfusion, exchange perfusion, and measures to increase urine production are considered unlikely to be of benefit.

Precautions

Duloxetine should not be used in patients with hepatic or severe renal impairment and is contra-indicated in patients with uncontrolled narrow-angle glaucoma or hypertension. Patients with raised intra-ocular pressure or at risk of angle-closure glaucoma should be monitored closely. Blood pressure should also be monitored because of the risk of hypertension. Increases in fasting blood glucose and in total cholesterol have been reported in diabetic patients. It should be used with caution in patients with a history of seizures, of bleeding disorders, or of hypomania or mania.

Patients should be closely monitored during early antidepressant therapy until significant improvement in depression is observed because suicide is an inherent risk in depressed patients. For further details, see under Depression, p.373. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be observed when treating patients with other disorders.

As with other antidepressants, duloxetine may impair performance of skilled tasks and, if affected, patients should not drive or operate machinery.

Symptoms reported when duloxetine therapy was stopped abruptly include headache, nausea, vomiting, dizziness, insomnia, anxiety, and paraesthesia. It is therefore recommended that duloxetine should be withdrawn gradually over at least 2 weeks after more than one week of therapy and the patient monitored to minimise the risk of withdrawal reactions.

Children. Duloxetine has not been studied for the treatment of depression in adolescents and children; consequently its use in patients under 18 years of age is not generally recommended. In addition, other antidepressants have been shown to increase the risk of suicidal thoughts and behaviour in such patients (see Effects on the Mental State, under Fluoxetine, p.392).

Interactions

Duloxetine should not be used with MAOIs and at least 14 days should elapse between stopping an MAOI and starting treatment with duloxetine. At least 5 days should elapse between stopping duloxetine and starting any drug liable to provoke a serious reaction (e.g. phenelzine). The use of duloxetine with other antidepressants including the SSRIs, other serotonin and noradrenaline reuptake inhibitors, and the reversible inhibitors of monoamine oxidase is not recommended. For further details, see Antidepressants under Interactions of Phenelzine, p.418.

Caution is advised when using duloxetine with other centrally acting drugs including alcohol and those with sedative properties.

Duloxetine is metabolised by the cytochrome P450 isoenzymes CYP1A2 and CYP2D6. It should not be given with potent inhibitors of CYP1A2 such as fluvoxamine, ciprofloxacin, and enoxacin as such combinations are likely to result in increased duloxetine concentrations. Similarly, caution is recommended when duloxetine is given with potent CYP2D6 inhibitors such as paroxetine. Duloxetine itself is also a moderate inhibitor of CYP2D6 and, consequently, licensed drug information recommends that it should be used cautiously with drugs that have a narrow therapeutic index and are extensively metabolised by this isoenzyme. In particular, use with thioridazine is contra-indicated because of the risk of serious ventricular arrhythmias and sudden death associated with raised thioridazine concentrations.

Duloxetine is highly protein bound and adverse effects may occur if given with other highly protein-bound drugs.

◊ References.

1. Skinner MH, *et al.* Duloxetine is both an inhibitor and a substrate of cytochrome P4502D6 in healthy volunteers. *Clin Pharmacol Ther* 2003; **73:** 170–7.
2. Lobo ED, *et al.* In vitro and in vivo evaluations of cytochrome P450 1A2 interactions with duloxetine. *Clin Pharmacokinet* 2008; **47:** 191–202.

Antimigraine drugs. There have been rare reports of serotonin syndrome associated with the use of serotonin and noradrenaline reuptake inhibitors (SNRIs) with serotonin ($5\text{-}HT_1$) agonists such as *sumatriptan* (see p.626).

Pharmacokinetics

Duloxetine is well absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 6 hours after an oral dose. Food delays the time to reach peak concentrations to 10 hours. Protein binding is about 96%, primarily to albumin and $alpha_1$-acid glycoprotein. Duloxetine is extensively metabolised by the cytochrome P450 isoenzymes CYP1A2 and CYP2D6; two major, but inactive, metabolites are formed, 4-hydroxy duloxetine glucuronide and 5-hydroxy, 6-methoxy duloxetine sulfate. These and other metabolites are principally excreted in the urine; about 20% is excreted in the faeces. Less than 1% of a dose is excreted in the urine as unchanged duloxetine. The elimination half-life of duloxetine is 8 to 17 hours with an average of about 12 hours. Duloxetine is distributed into breast milk.

◊ References.

1. Lantz RJ, *et al.* Metabolism, excretion, and pharmacokinetics of duloxetine in healthy human subjects. *Drug Metab Dispos* 2003; **31**: 1142–50.
2. Skinner MH, *et al.* Effect of age on the pharmacokinetics of duloxetine in women. *Br J Clin Pharmacol* 2004; **57:** 54–61.
3. Lobo ED, *et al.* Pharmacokinetics of duloxetine in breast milk and plasma of healthy postpartum women. *Clin Pharmacokinet* 2008; **47:** 103–9.

Uses and Administration

Duloxetine hydrochloride is a serotonin and noradrenaline reuptake inhibitor (SNRI) (see Venlafaxine, p.427). It is given orally as the hydrochloride although doses are expressed in terms of the base; duloxetine hydrochloride 22.5 mg is equivalent to about 20 mg of duloxetine.

Duloxetine is used in the treatment of **depression** in usual initial doses of 20 or 30 mg twice daily, or 60 mg once daily. A lower starting dose of 30 mg once daily for the first week may be suitable for some patients, to allow them to adjust to the effects of duloxetine before increasing the dose. A dose of 60 mg once daily may be used for maintenance therapy.

Duloxetine is also used in the treatment of **generalised anxiety disorder**, in a usual dose of 60 mg once daily. A lower starting dose of 30 mg daily for the first week may be considered in some patients, before increasing to 60 mg daily.

In the treatment of diabetic **peripheral neuropathic pain** the usual dose is 60 mg once daily. Some patients who respond insufficiently to this dose may benefit from up to 120 mg daily in divided doses. Response to therapy should be evaluated after 2 months and every 3 months thereafter.

Duloxetine is also used in the treatment of moderate to severe **stress urinary incontinence** in women. Usual initial doses are 40 mg twice daily; however, some patients may benefit from an initial dose of 20 mg twice daily for 2 weeks before increasing to 40 mg twice daily.

For dosage in hepatic or renal impairment, see below.

Duloxetine should be withdrawn gradually to reduce the risk of withdrawal symptoms (see Precautions, above).

Administration in hepatic or renal impairment. Duloxetine should not be used in patients with hepatic impairment. UK licensed product information for duloxetine states that no dosage adjustment is necessary in mild to moderate renal impairment (creatinine clearance 30 mL/minute or above). However, US information suggests that a lower starting dose and gradual dose increase may be warranted for patients, such as diabetics, with renal impairment. Both UK and US information recommend that duloxetine should not be used in more severe renal impairment (creatinine clearance less than 30 mL/minute).

Anxiety disorders. Duloxetine is used in the treatment of generalised anxiety disorder (see under Phobic Disorders, p.953).

References.

1. Koponen H, *et al.* Efficacy of duloxetine for the treatment of generalized anxiety disorder: implications for primary care physicians. *Prim Care Companion J Clin Psychiatry* 2007; **9:** 100–107.
2. Endicott J, *et al.* Duloxetine treatment for role functioning improvement in generalized anxiety disorder: three independent studies. *J Clin Psychiatry* 2007; **68:** 518–24. Corrections. *ibid.* 2007; 518, 806.
3. Hartford J, *et al.* Duloxetine as an SNRI treatment for generalized anxiety disorder: results from a placebo and active-controlled trial. *Int Clin Psychopharmacol* 2007; **22:** 167–74.
4. Allgulander C, *et al.* Pharmacotherapy of generalized anxiety disorder: results of duloxetine treatment from a pooled analysis of three clinical trials. *Curr Med Res Opin* 2007; **23:** 1245–52.
5. Rynn M, *et al.* Efficacy and safety of duloxetine in the treatment of generalized anxiety disorder: a flexible-dose, progressive-titration, placebo-controlled trial. *Depress Anxiety* 2008; **25:** 182–9.

Depression. As discussed on p.373, there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effect profile. SSRIs are widely used as an alternative to the older tricyclics as they have fewer adverse effects and are safer in overdosage. Similar properties may also favour the use of serotonin and noradrenaline reuptake inhibitors such as duloxetine.

References.

1. Goldstein DJ, *et al.* Duloxetine in the treatment of major depressive disorder: a double-blind clinical trial. *J Clin Psychiatry* 2002; **63:** 225–31.
2. Detke MJ, *et al.* Duloxetine, 60 mg once daily, for major depressive disorder: a randomized double-blind placebo-controlled trial. *J Clin Psychiatry* 2002; **63:** 308–15.
3. Raskin J, *et al.* Duloxetine in the long-term treatment of major depressive disorder. *J Clin Psychiatry* 2003; **64:** 1237–44.
4. Goldstein DJ, *et al.* Duloxetine in the treatment of depression: a double-blind placebo-controlled comparison with paroxetine. *J Clin Psychopharmacol* 2004; **24:** 389–99.
5. Detke MJ, *et al.* Duloxetine in the acute and long-term treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. *Eur Neuropsychopharmacol* 2004; **14:** 457–70.
6. Dugan SE, Fuller MA. Duloxetine: a dual reuptake inhibitor. *Ann Pharmacother* 2004; **38:** 2078–85.

Micturition disorders. Duloxetine is used[1-3] to increase urethral tone in the treatment of women with moderate to severe stress urinary incontinence (p.2180). A systematic review[3] concluded that duloxetine treatment reduced the frequency of incontinence episodes and significantly improved the patient's quality of life; however, it was unclear if these benefits were sustained. In addition, the review showed that adverse effects, particularly nausea, were common with duloxetine and led some patients to stop treatment.

1. McCormack PL, Keating GM. Duloxetine in stress urinary incontinence. *Drugs* 2004; **64:** 2567–73.
2. Ghoniem GM, *et al.* A randomized controlled trial of duloxetine alone, pelvic floor muscle training alone, combined treatment and no active treatment in women with stress urinary incontinence. *J Urol (Baltimore)* 2005; **173:** 1647–53.
3. Mariappan P, *et al.* Serotonin and noradrenaline reuptake inhibitors (SNRI) for stress urinary incontinence in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 14/09/06).

Pain. Duloxetine is used[1] in the treatment of diabetic peripheral neuropathic pain (p.6). It has also been tried[2] with some success in fibromyalgia (see Soft-tissue Rheumatism, p.13), a condition that responds poorly to analgesics and anti-inflammatory drugs.

1. Goldstein DJ, *et al.* Duloxetine vs placebo in patients with painful diabetic neuropathy. *Pain* 2005; **116:** 109–18.
2. Arnold LM, *et al.* A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. *Arthritis Rheum* 2004; **50:** 2974–84.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Cymbalta; Duxetin; ***Austral.:*** Cymbalta; ***Belg.:*** Cymbalta; Yentreve; ***Braz.:*** Cymbalta; ***Chile:*** Cymbalta; Yentreve; ***Cz.:*** Ariclaim; Cymbalta; Xeristar; Yentreve; ***Denm.:*** Cymbalta; Yentreve; ***Fin.:*** Cymbalta; Yentreve; ***Fr.:*** Cymbalta; Yentreve; ***Ger.:*** Cymbalta; Yentreve; ***Gr.:*** Ariclaim; Cymbalta; Xeristar; Yentreve; ***Hong Kong:*** Cymbalta; ***Hung.:*** Cymbalta; ***India:*** Delok; ***Indon.:*** Cymbalta; ***Irl.:*** Cymbalta; Yentreve; ***Israel:*** Cymbalta; ***Ital.:*** Ariclaim; Cymbalta; Xeristar; Yentreve; ***Malaysia:*** Cymbalta; ***Mex.:*** Cymbalta; Yentreve; ***Neth.:*** Ariclaim; Cymbalta; Xeristar; Yentreve; ***Norw.:*** Cymbalta; Yentreve; ***Philipp.:*** Cymbalta; ***Port.:*** Ariclaim; Cymbalta; Xeristar; Yentreve; ***Rus.:*** Cymbalta (Симбалта); ***S.Afr.:*** Cymbalta; ***Singapore:*** Cymbalta; ***Spain:*** Cymbalta; Xeristar; ***Swed.:*** Cymbalta; Yentreve; ***UK:*** Cymbalta; Yentreve; ***USA:*** Cymbalta.

Escitalopram Oxalate

(BANM, USAN, rINNM)

S-Citalopram Oxalate; Escitalopram, Oxalate d'; Escitalopramі Oxalas; Lu-26-054/0; Oxalato de escitalopram. (+)-(*S*)-1-[3-(dimethylamino)propyl]-1-(*p*-fluorophenyl)-5-phthalancarbonitrile oxalate.

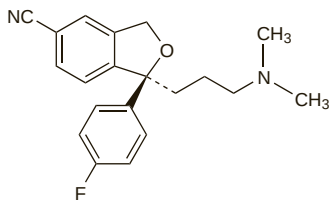
Эсциталопрама Оксалат

$C_{20}H_{21}FN_2O,C_2H_2O_4$ = 414.4.

CAS — 128196-01-0 (escitalopram); 219861-08-2 (escitalopram oxalate).

ATC — N06AB10.

ATC Vet — QN06AB10.



(escitalopram)

Adverse Effects and Precautions

As for Citalopram, p.385.

Children. SSRIs are associated with an increased risk of potentially suicidal behaviour when used for the treatment of depression in children and adolescents under 18 years old; for further details, see under Effects on Mental State in Fluoxetine, p.392.

Pharmacokinetics

Escitalopram has similar pharmacokinetics to those of racemic citalopram (p.385).

◊ References.

1. Søgaard B, *et al.* The pharmacokinetics of escitalopram after oral and intravenous administration of single and multiple doses to healthy subjects. *J Clin Pharmacol* 2005; **45:** 1400–6.
2. Rao N. The clinical pharmacokinetics of escitalopram. *Clin Pharmacokinet* 2007; **46:** 281–90.

Uses and Administration

Escitalopram, the *S*-enantiomer of citalopram (p.385), is an SSRI with actions and uses similar to those of fluoxetine (p.391). It is given orally as the oxalate although doses are expressed in terms of the base; escitalopram oxalate 12.8 mg is equivalent to about 10 mg of escitalopram.

In the treatment of **depression**, the usual dose is 10 mg once daily increased, after at least a week, to a maximum of 20 mg once daily if necessary.

Escitalopram is also used in the treatment of **panic disorder** with or without agoraphobia. Initial doses are 5 mg once daily, increased after a week to 10 mg once daily; further increases up to a maximum of 20 mg daily may be necessary in some patients.

Doses of escitalopram used in the treatment of **generalised anxiety disorder**, **social anxiety disorder**, and **obsessive-compulsive disorder** are similar to those used in depression.

Initial treatment with half the usual recommended dose and a lower maximum dose should be considered in elderly patients. Patients with hepatic impairment or those who are poor metabolisers with respect to the cytochrome P450 isoenzyme CYP2C19 may also require lower doses (see below).

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

Administration in hepatic impairment. Increases of 51% and 69% in the area under the concentration-time curve occurred in a single-dose study of escitalopram in patients with mild and moderate hepatic impairment (Child-Pugh score 5 or 6, and 7 to 9, respectively).[1] This study also reported that activity of the cytochrome P450 isoenzyme CYP2C19 was a better predictor of escitalopram clearance than the Child-Pugh classification.

UK licensed product information for escitalopram suggests that patients with mild to moderate hepatic impairment or those who are poor metabolisers with respect to the cytochrome P450 isoenzyme CYP2C19 should receive an initial oral dose of 5 mg daily, increased to 10 mg daily after 2 weeks depending on response; more careful dose titration is advised in those with severe impairment. US licensed product information recommends 10 mg daily as a suitable dose for most patients with hepatic impairment.

1. Areberg J, *et al.* The pharmacokinetics of escitalopram in patients with hepatic impairment. *AAPS J* 2006; **8:** E14–E19.

Anxiety disorders. Escitalopram has been given in anxiety disorders (p.952) including panic disorder (p.952), obsessive-compulsive disorder (p.952), and social anxiety disorder (see under Phobic Disorders, p.953).

References.

1. Stahl SM, *et al.* Escitalopram in the treatment of panic disorder: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 2003; **64:** 1322–7.
2. Davidson JR, *et al.* Escitalopram in the treatment of generalized anxiety disorder: double-blind, placebo controlled, flexible-dose study. *Depress Anxiety* 2004; **19:** 234–40.
3. Lader M, *et al.* Efficacy and tolerability of escitalopram in 12- and 24-week treatment of social anxiety disorder: randomised, double-blind, placebo-controlled, fixed-dose study. *Depress Anxiety* 2004; **19:** 241–8.
4. Kasper S, *et al.* Escitalopram in the treatment of social anxiety disorder: randomised, placebo-controlled, flexible-dosage study. *Br J Psychiatry* 2005; **186:** 222–6.
5. Stein DJ, *et al.* Escitalopram in obsessive-compulsive disorder: a randomized, placebo-controlled, paroxetine-referenced, fixed-dose, 24-week study. *Curr Med Res Opin* 2007; **23:** 701–11.

Depression. As discussed on p.373, there is very little difference in efficacy between the different groups of antidepressant drugs. SSRIs such as escitalopram are widely used as an alternative to the older tricyclics as they have fewer adverse effects and are safer in overdosage.

References.

1. Burke WJ, *et al.* Fixed-dose trial of the single isomer SSRI escitalopram in depressed outpatients. *J Clin Psychiatry* 2002; **63:** 331–6.
2. Wade A, *et al.* Escitalopram 10mg/day is effective and well tolerated in a placebo-controlled study in depression in primary care. *Int Clin Psychopharmacol* 2002; **17:** 95–102.
3. Lepola UM, *et al.* Escitalopram (10-20 mg/day) is effective and well tolerated in a placebo-controlled study in depression in primary care. *Int Clin Psychopharmacol* 2003; **18:** 211–17.
4. Rapaport MH, *et al.* Escitalopram continuation treatment prevents relapse of depressive episodes. *J Clin Psychiatry* 2004; **65:** 44–9.
5. Montgomery SA, *et al.* A randomised study comparing escitalopram with venlafaxine XR in primary care patients with major depressive disorder. *Neuropsychobiology* 2004; **50:** 57–64.
6. Murdoch D, Keam SJ. Escitalopram: a review of its use in the management of major depressive disorder. *Drugs* 2005; **65:** 2379–2404.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Aramix; Citalax; Lexapro; Lextor; Meridian; ***Austral.:*** Esipram; Lexapro; ***Austria:*** Cipralex; ***Belg.:*** Sipralexa; ***Braz.:*** Lexapro; ***Canad.:*** Cipralex; ***Chile:*** Celtium; Ectiban; Ipran; Lexapro; Neozentius; Zepaz; ***Cz.:*** Cipralex; ***Denm.:*** Cipralex; ***Fin.:*** Cipralex; ***Fr.:*** Seroplex; ***Ger.:*** Cipralex; ***Gr.:*** Cipralex; Entact; ***Hong Kong:*** Lexapro; ***Hung.:*** Cipralex; ***India:*** Cipralex; Recita; S-Citadep; ***Indon.:*** Cipralex; ***Irl.:*** Lexapro; ***Israel:*** Cipralex; ***Ital.:*** Cipralex; Entact; ***Malaysia:*** Lexapro; ***Mex.:*** Lexapro; ***Neth.:*** Cipralex; Lexapro; ***Norw.:*** Cipralex; ***NZ:*** Lexapro; ***Philipp.:*** Lexapro; ***Pol.:*** Lexapro; ***Port.:*** Cipralex; ***Rus.:*** Cipralex (Ципралекс); ***S.Afr.:*** Cipralex; ***Singapore:*** Lexapro; ***Spain:*** Cipralex; Entact; Esertia; ***Swed.:*** Cipralex; ***Switz.:*** Cipralex; ***Thai.:*** Lexapro; ***Turk.:*** Cipralex; ***UK:*** Cipralex; ***USA:*** Lexapro; ***Venez.:*** Lexapro.

Fluoxetine Hydrochloride

(BANM, USAN, rINNM)

Fluoksetiinihydrokloridi; Fluoksetin Hidroklorür; Fluoksetino hidrochloridas; Fluoksetyny chlorowodorek; Fluoxétine, chlorhydrate de; Fluoxetin-hidroklorid; Fluoxetin-hydrochlorid; Fluoxetinhydroklorid; Fluoxetini hydrochloridum; Hidrocloruro de fluoxetina; Lilly-103472; LY-110140. (±)-*N*-Methyl-3-phenyl-3-(α,α,α-trifluoro-*p*-tolyloxy)propylamine hydrochloride.

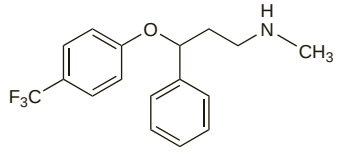
Флуоксетина Гидрохлорид

$C_{17}H_{18}F_3NO,HCl$ = 345.8.

CAS — 54910-89-3 (fluoxetine); 59333-67-4 (fluoxetine hydrochloride).

ATC — N06AB03.

ATC Vet — QN06AB03.



(fluoxetine)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of fluoxetine:
Distas; Green and whites; Greens; Limes; Pros; Zacs.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Fluoxetine Hydrochloride). A white or almost white crystalline powder. Sparingly soluble in water and in dichloromethane; freely soluble in methyl alcohol. A 1% solution in water has a pH of 4.5 to 6.5.

USP 31 (Fluoxetine Hydrochloride). A white to off-white crystalline powder. Sparingly soluble in water and in dichloromethane; freely soluble in alcohol and in methyl alcohol; practically insoluble in ether. Store in airtight containers.

Adverse Effects

SSRIs such as fluoxetine are less sedating than tricyclic antidepressants and have fewer antimuscarinic and cardiotoxic effects. Adverse effects reported with SSRIs include dry mouth and gastrointestinal disturbances such as nausea, vomiting, dyspepsia, constipation, and diarrhoea. Anorexia and weight loss may also occur. Neurological adverse effects have included either anxiety, restlessness, nervousness, and insomnia, or drowsiness and fatigue; headache, tremor, dizziness, seizures, hallucinations, confusion, agitation, extrapyramidal effects, depersonalisation, mania, panic attacks, sexual dysfunction, and symptoms suggestive of a serotonin syndrome (p.416) have also occurred. The concern that SSRIs may be associated with increased suicidal ideation is discussed under Effects on Mental State, below.

Excessive sweating, pruritus, skin rashes, alopecia, photosensitivity, and urticaria have also been reported. Angioedema and anaphylactoid reactions have occurred. In some patients who have developed rashes while taking fluoxetine, systemic hypersensitivity reactions involving the lungs, kidneys, or liver, and possibly related to vasculitis, have developed; it has therefore been advised that fluoxetine therapy should be stopped in any patient who develops a skin rash.

Hyponatraemia, possibly due to inappropriate secretion of antidiuretic hormone, has been associated with the use of antidepressants, particularly in the elderly. Hyperprolactinaemia and galactorrhoea have occurred, as have changes in blood sugar, in patients receiving SSRIs.

Arthralgia and myalgia have been reported and there have also been cases of orthostatic hypotension, yawning, urinary retention, and abnormal vision including blurred vision and mydriasis. Abnormal liver function tests have been reported rarely. SSRIs have occasionally been associated with bleeding disorders such as ecchymosis and purpura and other effects on the blood.

In overdosage nausea, vomiting, and excitation of the CNS are considered to be prominent features; death has been reported.

Incidence of adverse effects. In June 1992 the UK CSM had received 1236 reports of adverse effects with fluvoxamine (from about 280 000 prescriptions) compared with 2422 for fluoxetine (from about 480 000 prescriptions).[1] The overall patterns of adverse effects were similar but dermatological reactions were more likely with fluoxetine and gastrointestinal reactions with fluvoxamine. Reports of attempted suicide increased after adverse publicity about SSRIs in 1990, and the number of reports per million prescriptions were similar for the 2 drugs (25 for fluoxetine and 20 for fluvoxamine); at that time such figures were not considered disconcerting given that features of depression, including attempted suicide, can worsen after the introduction of any antidepressant (see also Effects on Mental State, below). A later review[2] by the CSM of the 5 SSRIs available in the UK (citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) found that the SSRIs were broadly similar with respect to their safety profile. A list of adverse reactions common to all SSRIs was provided.

A review[3] of 1861 adverse reactions to citalopram, fluoxetine, fluvoxamine, paroxetine, or sertraline reported to the Swedish Adverse Drug Reactions Advisory Committee found that the most commonly reported reactions were neurological (22.4% of all reports), psychiatric (19.5%), and gastrointestinal (18.0%). Compared with other SSRIs, gastrointestinal symptoms were more common with fluvoxamine, psychiatric symptoms with sertraline, and dermatological symptoms with fluoxetine.

A more recent meta-analysis[4] has compared the adverse effect profile of fluoxetine with other antidepressants including the tricyclics and other SSRIs. The overall risk of any adverse effect with fluoxetine was less than that for the tricyclic antidepressants; however, there was no difference in risk when fluoxetine was compared with other SSRIs. When considering individual adverse reactions, fluoxetine was more likely to cause activating