therapy with the non-selective inhibitors is particularly unsuitable for patients considered unable to adhere to the strict dietary requirements necessary for safe usage. (For contra-indication in children, see under Precautions, above).

Phenelzine is given orally as the sulfate although doses are expressed in terms of the base. Phenelzine sulfate 25.8 mg is equivalent to about 15 mg of phenelzine. The usual initial dose is equivalent to phenelzine 15 mg three times daily; if no response has been obtained after 2 weeks the dosage may be increased to 15 mg four times daily; severely depressed patients in hospital may be given up to 30 mg three times daily. Once a response has been obtained the dosage may be gradually reduced for maintenance therapy; some patients may continue to respond to 15 mg on alternate days.

Phenelzine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Anxiety disorders. MAOIs have been used in the treatment of anxiety disorders. MAOIs appear to be effective in *panic disorder* (p.952). They also appear to be effective in *social anxiety disorder* (see under Phobic Disorders, p.953) and can improve anticipatory anxiety and functional disability. The main treatment for *post-traumatic stress disorder* (p.953) is psychotherapy but MAOIs are one of the alternatives that can help to reduce traumatic recollections and nightmares, and to repress flashbacks.

References.

1. Buigues J, Vallejo J. Therapeutic response to phenelzine in patients with panic disorder and agoraphobia with panic attacks. *J Clin Psychiatry* 1987; **48:** 55–9.
2. Frank JB, *et al.* A randomized clinical trial of phenelzine and imipramine for posttraumatic stress disorder. *Am J Psychiatry* 1988; **145:** 1289–91.
3. Heimberg RG, *et al.* Cognitive behavioural group therapy vs phenelzine therapy for social phobia: 12 week outcome. *Arch Gen Psychiatry* 1998; **55:** 1133–41.
4. Aarre TF. Phenelzine efficacy in refractory social anxiety disorder: a case series. *Nord J Psychiatry* 2003; **57:** 313–15.

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 effects. MAOIs are rarely used as first-choice antidepressants because of the dangers of dietary and drug interactions. Even in depressed patients with atypical, hypochondriacal, hysterical, or phobic features, for which MAOIs are particularly effective, it is often recommended that another antidepressant type should be tried first. Reversible inhibitors of monoamine oxidase type A (RIMAs) offer an alternative to the MAOIs and less strict dietary restrictions are necessary. They may be effective in a wide range of depressive disorders, although their relative efficacy in atypical depression remains to be established.

Combination therapy with differing classes of antidepressants, including the MAOIs, has been used in the treatment of drug-resistant depression. However, such therapy may result in enhanced adverse reactions or interactions and is considered unsuitable or controversial by some. For further details, see Antidepressants under Interactions, above.

Hyperactivity. When drug therapy is required for attention deficit hyperactivity disorder (p.2148), initial treatment is usually with a central stimulant. MAOIs have been used successfully but problems with dietary restriction and potential drug interactions have limited their use.

Migraine. A number of drugs have been used for the prophylaxis of migraine (p.616), although propranolol is generally preferred. Antidepressants such as the tricyclics can be useful alternatives when these drugs are ineffective or unsuitable. MAOIs are best reserved for severe cases refractory to other forms of prophylactic treatment.

Preparations

BP 2008: Phenelzine Tablets;
USP 31: Phenelzine Sulfate Tablets.

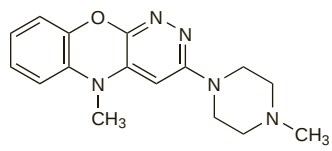
Proprietary Preparations (details are given in Part 3)
Austral.: Nardil; ***Belg.:*** Nardelzine; ***Canad.:*** Nardil; ***Irl.:*** Nardil; ***NZ:*** Nardil; ***UK:*** Nardil; ***USA:*** Nardil.

Pipofezine Hydrochloride *(rINNM)*

Hidrocloruro de pipofezina; Pipofézine, Chlorhydrate de; Pipofezine Dihydrochloride; Pipofezini Hydrochloridum. 5-Methyl-3-(4-methyl-1-piperazinyl)-5*H*-pyridazino[3,4-*b*][1,4]benzoxazine dihydrochloride.

Пипофезина Гидрохлорид

$C_{16}H_{19}N_5O,2HCl$ = 370.3.
CAS — 24886-52-0 (pipofezine); 24853-80-3 (pipofezine hydrochloride).



(pipofezine)

Profile

Pipofezine is a tricyclic antidepressant (see Amitriptyline, p.376).

In the treatment of depression (p.373) pipofezine is usually given orally as the hydrochloride although doses are expressed in terms of the base; pipofezine hydrochloride 31.1 mg is equivalent to about 25 mg of pipofezine. An initial dose is 25 mg given four times daily, increased to an optimum total daily dose of 150 to 200 mg; if necessary up to a maximum of 500 mg may be given daily in divided doses. For maintenance a modified-release preparation providing pipofezine 150 mg may be given once or twice daily.

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

Preparations

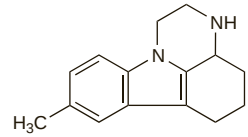
Proprietary Preparations (details are given in Part 3)
Rus.: Azaphen (Азафен).

Pirlindole *(rINN)*

Pirlindol; Pirlindolum. 2,3,3a,4,5,6-Hexahydro-8-methyl-1*H*-pyrazino[3,2,1-*jk*]carbazole.

Пирлиндол

$C_{15}H_{18}N_2$ = 226.3.
CAS — 60762-57-4.



Profile

Pirlindole has been given by mouth in the treatment of depression.

Preparations

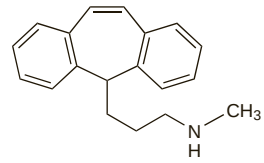
Proprietary Preparations (details are given in Part 3)
Port.: Implementor; ***Rus.:*** Pyrazidol (Пиразидол).

Protriptyline Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de protriptilina; MK-240; Protriptyline, chlorhydrate de; Protriptylini hydrochloridum. 3-(5*H*-Dibenzo[*a,d*]cyclohept-5-enyl)propyl(methyl)amine hydrochloride.

Протриптилина Гидрохлорид

$C_{19}H_{21}N,HCl$ = 299.8.
CAS — 438-60-8 (protriptyline); 1225-55-4 (protriptyline hydrochloride).
ATC — N06AA11.
ATC Vet — QN06AA11.



(protriptyline)

Pharmacopoeias. In *Br.* and *US.*

BP 2008 (Protriptyline Hydrochloride). A white to yellowish-white, odourless or almost odourless, powder. Freely soluble in water, in alcohol, and in chloroform; practically insoluble in ether. A 1% solution in water has a pH of 5.0 to 6.5.

USP 31 (Protriptyline Hydrochloride). A white to yellowish powder. Is odourless or has not more than a slight odour. Soluble 1 in 2 of water, 1 in 3.5 of alcohol, and 1 in 2.5 of chloroform; practically insoluble in ether. pH of a 1% solution in water is between 5.0 and 6.5.

Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p.376).

Since protriptyline may have some stimulant properties anxiety and agitation can occur more frequently; cardiovascular effects such as tachycardia and orthostatic hypotension may also be more frequent than with other tricyclics. Photosensitivity rashes have been noted more often with protriptyline than with other tricyclic antidepressants and patients taking it should avoid direct sunlight.

Interactions

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

Pharmacokinetics

Protriptyline is well but slowly absorbed after oral doses: licensed drug information states that peak plasma concentrations are achieved only after 8 to 12 hours.

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

Protriptyline is widely distributed throughout the body and extensively bound to plasma and tissue protein. Protriptyline has been estimated to have a very prolonged elimination half-life ranging from 55 to 198 hours, which may be further prolonged in overdosage.

Uses and Administration

Protriptyline is a dibenzocycloheptatriene tricyclic antidepressant with actions and uses similar to those of amitriptyline (p.381). It is considerably less sedative than other tricyclics and may have a stimulant effect, thus making it particularly suitable for apathetic and withdrawn patients; its antimuscarinic effects are moderate.

In the treatment of depression, protriptyline hydrochloride is given in oral doses of 5 to 10 mg three or four times daily. It has been suggested that, because of its potential stimulant activity, any dosage increases should be added to the morning dose first and if insomnia occurs the last dose should be given no later than mid-afternoon. Higher doses of up to 60 mg daily may be required in severely depressed patients. A suitable initial dose for adolescents and the elderly is 5 mg three times daily; close monitoring of the cardiovascular system has been recommended if the dose exceeds a total of 20 mg daily in elderly subjects.

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

Preparations

BP 2008: Protriptyline Tablets;
USP 31: Protriptyline Hydrochloride Tablets.

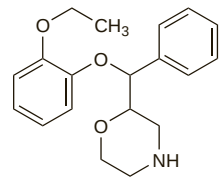
Proprietary Preparations (details are given in Part 3)
USA: Vivactil.

Reboxetine Mesilate *(BANM, rINNM)*

FCE-20124 (reboxetine or reboxetine mesilate); Mesilato de reboxetina; PNU-155950E; Réboxétine, Mésilate de; Reboxetine Mesylate *(USAN)*; Reboxetini Mesilas. (±)-(2*RS*)-2-[(α*RS*)-α-(2-Ethoxyphenoxy)benzyl]morpholine methanesulphonate.

Ребоксетина Мезилат

$C_{19}H_{23}NO_3,CH_4O_3S$ = 409.5.
CAS — 71620-89-8; 98769-81-4 (both reboxetine); 98769-82-5; 98769-84-7 (both reboxetine mesilate).
ATC — N06AX18.
ATC Vet — QN06AX18.



(reboxetine)

Adverse Effects

Adverse effects most commonly seen with reboxetine include insomnia, dry mouth, constipation, and increased sweating. Disturbance of visual accommodation, loss of appetite, vertigo, tachycardia, palpitations, vasodilatation, orthostatic hypotension, urinary hesitancy or retention (mainly in men), and erectile dysfunction including ejaculatory delay are also reported as being common adverse reactions. There have been reports of allergic dermatitis, convulsions, aggressive behaviour, cold extremities, and nausea and vomiting. Reduced plasma-potassium concentrations have been seen in elderly patients after prolonged use.

Hyponatraemia, possibly as a result of inappropriate secretion of antidiuretic hormone, has been associated with the use of antidepressants, particularly in the elderly.

Effects on the CNS. Episodes of sleepwalking (somnambulism) were seen in an 18-year-old woman several weeks after starting reboxetine (at an initial dose of 2 mg daily gradually increased to 8 mg daily).[1] The patient had a history of childhood somnambulism that had resolved spontaneously; these particular episodes ceased after the dose of reboxetine was reduced to 4 mg daily.

1. Künzel HE, *et al.* Sleepwalking associated with reboxetine in a young female patient with major depression: a case report. *Pharmacopsychiatry* 2004; **37:** 307–8.

Effects on the endocrine system. Hyponatraemia thought to be associated with reboxetine therapy and to be due to the syndrome of inappropriate antidiuretic hormone secretion, has been reported in an elderly patient.[1]

1. Ranieri P, *et al.* Reboxetine and hyponatremia. *N Engl J Med* 2000; **342:** 215–16.

Effects on sexual function. The Australian Adverse Drug Reactions Advisory Committee has received 130 reports of adverse reactions associated with reboxetine use;[1] of these, 22 described male sexual dysfunction including ejaculation disorder (7), erectile dysfunction (4), and testicular pain or swelling (10). In addition there were 2 reports of increased libido in women.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Genitourinary symptoms with reboxetine. *Aust Adverse Drug React Bull* 2005; **24:** 10. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0506.pdf (accessed 24/11/05)

Effects on the urinary system. The Australian Adverse Drug Reactions Advisory Committee has received 26 reports of urinary symptoms such as hesitancy, reduced urine flow, and retention in patients taking reboxetine.[1] Although the majority of cases occurred in male patients, 6 reports mentioned such symptoms in women.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Genitourinary symptoms with reboxetine. *Aust Adverse Drug React Bull* 2005; **24:** 10. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0506.pdf (accessed 24/11/05)

Treatment of Adverse Effects

Symptomatic and supportive therapy should be given as required; activated charcoal may be given to adults who have ingested more than 40 mg of reboxetine, and to children, if they present within 1 hour of ingestion. Heart rhythm should be monitored if changes in blood pressure occur.

Genito-urinary disorders. Tamsulosin has been used successfully in the treatment of urinary hesitancy and painful ejaculation associated with reboxetine (see p.2197).

Precautions

Reboxetine should be used with caution in patients with renal or hepatic impairment. It should also be used under close supervision in patients with bipolar disorder, urinary retention, benign prostatic hyperplasia, glaucoma, or a history of epilepsy or cardiac disorders.

Patients should be closely monitored during early 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.

Ability to perform tasks requiring motor or cognitive skills or judgement may be impaired by reboxetine and patients, if affected, should not drive or operate machinery.

Children. Reboxetine has not been studied for the treatment of depression in children and consequently its use in such patients is not recommended by UK licensed product information. In addition, other antidepressants have been shown to increase the risk of suicidal thoughts and behaviour in children and adolescents (see Effects on Mental State, under Fluoxetine, p.392).

The elderly. Reboxetine is not recommended by UK licensed product information for use in elderly patients, because of a lack of experience in this patient group. However, reboxetine 2 mg twice daily by mouth was well tolerated in a study in 16 elderly patients (mean age 77.5 years) with post-stroke depression.[1]

1. Rampello L, *et al.* An evaluation of efficacy and safety of reboxetine in elderly patients affected by "retarded" post-stroke depression: a random, placebo-controlled study. *Arch Gerontol Geriatr* 2005; **40:** 275–85.

Interactions

Reboxetine should not be taken with, or within 2 weeks of stopping, an MAOI; at least one week should elapse after stopping reboxetine therapy before starting any drug liable to provoke a serious reaction (e.g. phenelzine). Caution should be exercised when reboxetine is given with other drugs that lower blood pressure because orthostatic hypotension has occurred with reboxetine. However, the use of reboxetine with ergot derivatives may cause an increase in blood pressure. The possibility of hypokalaemia if reboxetine is given with potassium-depleting diuretics should also be considered.

Reboxetine is primarily metabolised by the cytochrome P450 isoenzyme CYP3A4 and potent inhibitors of this isoenzyme may limit the elimination of reboxetine. Consequently, reboxetine should not be given with drugs known to inhibit CYP3A4 such as azole antifungals (e.g. ketoconazole), macrolide antibacterials (e.g. erythromycin) or fluvoxamine. Reboxetine in high concentrations has also been shown *in vitro* to inhibit CYP3A4 and CYP2D6; however studies *in vivo* have suggested that interactions with drugs metabolised by these isoenzymes are unlikely.

Antifungals. Plasma levels of reboxetine were significantly increased when given with *ketoconazole*.[1] The interaction was said to have involved the inhibition of the cytochrome P450 isoenzyme CYP3A4 by ketoconazole.

1. Herman BD, *et al.* Ketoconazole inhibits the clearance of the enantiomers of the antidepressant reboxetine in humans. *Clin Pharmacol Ther* 1999; **66:** 374–9.

Pharmacokinetics

Reboxetine is well absorbed from the gastrointestinal tract with peak plasma levels occurring after about 2 hours. Plasma protein binding is about 97% (92% in elderly subjects). *In-vitro* studies indicate that reboxetine is metabolised by the cytochrome P450 isoenzyme CYP3A4; the main metabolic pathways identified are dealkylation, hydroxylation, and oxidation followed by glucuronide or sulfate conjugation. Elimination is mainly via urine (78%) with 10% excreted as unchanged drug. The plasma elimination half-life is 13 hours. Data from *animal* studies indicate that reboxetine crosses the placenta and is distributed into breast milk.

◊ References.

1. Dostert P, *et al.* Review of the pharmacokinetics and metabolism of reboxetine, a selective noradrenaline reuptake inhibitor. *Eur Neuropsychopharmacol* 1997; **7** (suppl 1): S23–S35.
2. Fleishaker JC. Clinical pharmacokinetics of reboxetine, a selective norepinephrine reuptake inhibitor for the treatment of patients with depression. *Clin Pharmacokinet* 2000; **39:** 413–27.
3. Coulomb F, *et al.* Pharmacokinetics of single-dose reboxetine in volunteers with renal insufficiency. *J Clin Pharmacol* 2000; **40:** 482–7.
4. Poggesi I, *et al.* Pharmacokinetics of reboxetine in elderly patients with depressive disorders. *Int J Clin Pharmacol Ther* 2000; **38:** 254–9.

Uses and Administration

Reboxetine is a selective and potent inhibitor of the reuptake of noradrenaline; it also has a weak effect on serotonin reuptake. Reboxetine has no significant affinity for muscarinic receptors. It is given orally as the mesilate for the treatment of depression with doses expressed as the base. Reboxetine mesilate 5.2 mg is equivalent to about 4 mg of reboxetine. The dose of reboxetine is 4 mg twice daily, which may be increased after 3 to 4 weeks, if necessary, to 10 mg daily; the maximum daily dose should not exceed 12 mg. Reduced doses should be given in hepatic or renal impairment, see below. Reboxetine is not recommended for use in elderly patients (see under Precautions, above).

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

Administration in hepatic or renal impairment. Lower initial oral doses equivalent to 2 mg of reboxetine twice daily are recommended by UK licensed product information in hepatic or renal impairment; doses may be increased thereafter according to tolerance.

Anxiety disorders. Reboxetine has been tried with some benefit in panic disorder (p.952) although it may be less effective than the SSRIs.

References.

1. Versiani M, *et al.* Reboxetine, a selective norepinephrine reuptake inhibitor, is an effective and well-tolerated treatment for panic disorder. *J Clin Psychiatry* 2002; **63:** 31–7.
2. Seedat S, *et al.* Reboxetine and citalopram in panic disorder: a single-blind, cross-over, flexible-dose pilot study. *Int Clin Psychopharmacol* 2003; **18:** 279–84.
3. Bertani A, *et al.* Comparison of the treatment with paroxetine and reboxetine in panic disorder: a randomized, single-blind study. *Pharmacopsychiatry* 2004; **37:** 206–10.

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. Reboxetine, a selective inhibitor of noradrenaline reuptake, has a slightly different biochemical profile from both the tricyclics and the SSRIs; however, like the SSRIs, reboxetine appears to have fewer unpleasant adverse effects and to be safer in overdosage in comparison with the older tricyclics.

References.

1. Versiani M, *et al.* Reboxetine, a unique selective NRI, prevents relapse and recurrence in long-term treatment of major depressive disorder. *J Clin Psychiatry* 1999; **60:** 400–406.
2. Holm KJ, Spencer CM. Reboxetine: a review of its use in depression. *CNS Drugs* 1999; **12:** 65–83.
3. Scates AC, Doraiswamy PM. Reboxetine: a selective norepinephrine reuptake inhibitor for the treatment of depression. *Ann Pharmacother* 2000; **34:** 1302–12.
4. Versiani M, *et al.* Double-blind, placebo-controlled study with reboxetine in inpatients with severe major depressive disorder. *J Clin Psychopharmacol* 2000; **20:** 28–34.
5. Ferguson JM, *et al.* Effects of reboxetine on Hamilton Depression Rating Scale factors from randomized, placebo-controlled trials in major depression. *Int Clin Psychopharmacol* 2002; **17:** 45–51.
6. Andreoli V, *et al.* Reboxetine, a new noradrenaline selective antidepressant, is at least as effective as fluoxetine in the treatment of depression. *J Clin Psychopharmacol* 2002; **22:** 393–9.
7. Montgomery S, *et al.* The antidepressant efficacy of reboxetine in patients with severe depression. *J Clin Psychopharmacol* 2003; **23:** 45–50.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Prolift†; ***Austral.:*** Edronax; ***Austria:*** Edronax; ***Belg.:*** Edronax; ***Braz.:*** Prolift; ***Chile:*** Prolift; ***Cz.:*** Edronax†; ***Denm.:*** Edronax; ***Fin.:*** Edronax; ***Ger.:*** Edronax; Solvex; ***Hung.:*** Edronax; ***India:*** Narebox; ***Irl.:*** Edronax; ***Israel:*** Edronax; ***Ital.:*** Davedax; Edronax; ***Mex.:*** Edronax; ***Norw.:*** Edronax; ***NZ:*** Edronax; ***Pol.:*** Edronax; ***Port.:*** Edronax; ***S.Afr.:*** Edronax; ***Spain:*** Irenor; Norebox; ***Swed.:*** Edronax; ***Switz.:*** Edronax; ***Turk.:*** Edronax; ***UK:*** Edronax; ***Venez.:*** Prolift†.

Sertraline Hydrochloride

(BANM, USAN, rINNM)

CP-51974-01; CP-51974-1; Hidrocloruro de sertralina; Sertraline, chlorhydrate de; Sertralini hydrochloridum. (1*S*,4*S*)-4-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthyl(methyl)amine hydrochloride.

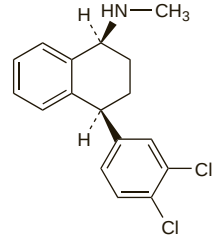
Сертралина Гидрохлорид

$C_{17}H_{17}Cl_2N,HCl$ = 342.7.

CAS — 79617-96-2 (sertraline); 79559-97-0 (sertraline hydrochloride).

ATC — N06AB06.

ATC Vet — QN06AB06.



(sertraline)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of sertraline: Z's; Zloft; Zoomers.

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

Ph. Eur. 6.2 (Sertraline Hydrochloride). A white or almost white, crystalline powder. It exhibits polymorphism. Slightly soluble in water; freely soluble in anhydrous alcohol; slightly soluble in acetone and in isopropyl alcohol. Protect from light.

Adverse Effects, Treatment, and Precautions

As for SSRIs in general (see Fluoxetine, p.391). Menstrual irregularities and, rarely, erythema multiforme and pancreatitis have also been reported.