A full blood count is recommended every 4 weeks during the first 3 months of treatment with mianserin, because of the risk of bone-marrow depression. Similarly, if a patient receiving mianserin develops fever, sore throat, stomatitis, or other signs of infection, treatment should be stopped and a full blood count obtained. The elderly are considered to be at special risk of blood disorders from mianserin. For further details see Effects on the Blood under Adverse Effects, above.

UK licensed drug information recommends that mianserin should not be given during breast feeding, but the *BNF* considers the amount distributed into breast milk too small to be harmful.

Porphyria. Mianserin hydrochloride is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Interactions

It is recommended that mianserin should not be given to patients receiving MAOIs or for at least 14 days afterwards. At least one week should elapse between withdrawing mianserin and starting any drug liable to provoke a serious reaction (e.g. phenelzine). Unlike the tricyclics (p.379), mianserin does not diminish the effects of the antihypertensives guanethidine, hydralazine, propranolol, or clonidine. However, it is still recommended that blood pressure be monitored when mianserin is prescribed with antihypertensive therapy. Plasma-phenytoin concentrations should be monitored carefully in patients also treated with mianserin; phenytoin has also been reported to reduce concentrations of mianserin (see below). There may be potentiation of effects when mianserin is given with CNS depressants such as alcohol, anxiolytics, or antipsychotics.

Antiepileptics. Reduced plasma concentrations and half-lives of mianserin and desmethylmianserin were seen in 6 patients also receiving antiepileptic therapy consisting of *phenytoin* with either *carbamazepine* or *phenobarbital*.[1] Carbamazepine alone may also reduce the plasma concentration of mianserin.[2,3]

Mianserin may antagonise the action of antiepileptics by lowering the convulsive threshold.

1. Nawishy S, *et al*. Kinetic interaction of mianserin in epileptic patients on anticonvulsant drugs. *Br J Clin Pharmacol* 1982; **13:** 612P–13P.
2. Leinonen E, *et al*. Effects of carbamazepine on serum antidepressant concentrations in psychiatric patients. *J Clin Psychopharmacol* 1991; **11:** 313–18.
3. Eap CB, *et al*. Effects of carbamazepine coadministration on plasma concentrations of the enantiomers of mianserin and of its metabolites. *Ther Drug Monit* 1999; **21:** 166–70.

Pharmacokinetics

Mianserin is readily absorbed from the gastrointestinal tract, but its bioavailability is reduced by extensive first-pass metabolism in the liver.

Paths of metabolism of mianserin include aromatic hydroxylation, *N*-oxidation, and *N*-demethylation. Desmethylmianserin and 8-hydroxymianserin are pharmacologically active.

Mianserin is excreted in the urine, almost entirely as its metabolites, either free or in conjugated form; some is also found in the faeces.

Mianserin is widely distributed throughout the body and is extensively bound to plasma proteins. It has been found to have a biphasic plasma half-life with the duration of the terminal phase ranging from about 6 to 40 hours. Mianserin crosses the blood-brain barrier and the placenta. It is distributed into breast milk.

◊ References.

1. Hrdina PD, *et al*. Mianserin kinetics in depressed patients. *Clin Pharmacol Ther* 1983; **33:** 757–62.
2. Pinder RM, Van Delft AML. The potential therapeutic role of enantiomers and metabolites of mianserin. *Br J Clin Pharmacol* 1983; **15:** 269S–276S.
3. Timmer CJ, *et al*. Absolute bioavailability of mianserin tablets and solution in healthy humans. *Eur J Drug Metab Pharmacokinet* 1985; **10:** 315–23.
4. Begg EJ, *et al*. Variability in the elimination of mianserin in elderly patients. *Br J Clin Pharmacol* 1989; **27:** 445–51.
5. Buist A, *et al*. Mianserin in breast milk. *Br J Clin Pharmacol* 1993; **36:** 133–4.
6. Dahl M-L, *et al*. Stereoselective disposition of mianserin is related to debrisoquin hydroxylation polymorphism. *Clin Pharmacol Ther* 1994; **56:** 176–83.

Uses and Administration

Mianserin is a tetracyclic antidepressant. It does not appear to have significant antimuscarinic properties, but has a marked sedative action. Unlike the tricyclic antidepressants (see Amitriptyline, p.381), mianserin does not prevent the peripheral reuptake of noradrenaline; it blocks presynaptic adrenergic (α_2) receptors and increases the turnover of brain noradrenaline. Mianserin is also an antagonist of postsynaptic serotonin receptors in some parts of the brain.

In the treatment of depression (p.373) mianserin hydrochloride is given in initial oral doses of 30 to 40 mg daily increased gradually thereafter as necessary. The effective daily dosage is usually between 30 and 90 mg. The daily dosage may be divided throughout the day or given as a single dose at night. Divided daily dosages of up to 200 mg have been given. The recommended initial daily dose in the elderly is not more than 30 mg, which may be slowly increased if necessary.

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

Preparations

BP 2008: Mianserin Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Lerivon; ***Austral.:*** Lumin; Tolvon; ***Austria:*** Miabene†; Tolvon; ***Belg.:*** Lerivon; ***Braz.:*** Tolvon; ***Chile:*** Athimil; Prevalina; ***Cz.:*** Lerivon; Miabene; ***Denm.:*** Tolmin; Tolvon; ***Fin.:*** Miaxan; Tolvon; ***Fr.:*** Athymil; ***Ger.:*** Hopacem†; Mianeurin; Prisma†; Tolvin; ***Hong Kong:*** Tolvon; ***Hung.:*** Tolvon; ***India:*** Depnon; ***Irl.:*** Tolvon; ***Israel:*** Bonserin; ***Ital.:*** Lantanon; ***Mex.:*** Tolvon; ***Neth.:*** Tolvon; ***Norw.:*** Tolvon; ***NZ:*** Tolvon; ***Pol.:*** Lerivon; Miansemerck; Norserin; ***Port.:*** Tolvon; ***Rus.:*** Lerivon (Леривон); ***S.Afr.:*** Lantanon; ***Spain:*** Lantanon; ***Swed.:*** Tolvon; ***Switz.:*** Amirine; Tolvon; ***Thai.:*** Mealin; Ornate†; Servin; Tolimed; Tolvon; ***Turk.:*** Tolvon; ***Venez.:*** Athimil†.

Milnacipran Hydrochloride *(BANM, rINNM)*

F-2207 (milnacipran); Hidrocloruro de milnaciprán; Midalcipran Hydrochloride; Milnacipran, Chlorhydrate de; Milnaciprani Hydrochloridum. (±)-*cis*-2-(Aminomethyl)-*N*,*N*-diethyl-1-phenylcyclopropanecarboxamide hydrochloride.

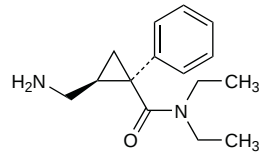
Мильнаципрана Гидрохлорид

$C_{15}H_{22}N_2O,HCl$ = 282.8.

CAS — 92623-85-3 (milnacipran); 101152-94-7 (milnacipran hydrochloride); 175131-61-0 (milnacipran hydrochloride).

ATC — N06AX17.

ATC Vet — QN06AX17.



(milnacipran)

Profile

Milnacipran hydrochloride is a serotonin and noradrenaline reuptake inhibitor (SNRI) (see Venlafaxine, p.427) used for the treatment of depression (p.373). It is given in usual oral doses of 50 mg twice daily. Milnacipran is also being investigated in the treatment of fibromyalgia.

◊ References.

1. Tignol J, *et al*. Double-blind study of the efficacy and safety of milnacipran and imipramine in elderly patients with major depressive episode. *Acta Psychiatr Scand* 1998; **97:** 157–65.
2. Spencer CM, Wilde MI. Milnacipran: a review of its use in depression. *Drugs* 1998; **56:** 405–27.
3. Rouillon F, *et al*. Milnacipran efficacy in the prevention of recurrent depression: a 12-month placebo-controlled study. *Int Clin Psychopharmacol* 2000; **15:** 133–40.
4. Clerc G. Antidepressant efficacy and tolerability of milnacipran, a dual serotonin and noradrenaline reuptake inhibitor: a comparison with fluvoxamine. *Int Clin Psychopharmacol* 2001; **16:** 145–51.
5. Fukuchi T, Kanemoto K. Differential effects of milnacipran and fluvoxamine, especially in patients with severe depression and agitated depression: a case-control study. *Int Clin Psychopharmacol* 2002; **17:** 53–8.
6. Vitton O, *et al*. A double-blind placebo-controlled trial of milnacipran in the treatment of fibromyalgia. *Hum Psychopharmacol* 2004; **19** (suppl 1): S27–S35.

Interactions. ***ANTIMIGRAINE DRUGS.*** There have been rare reports of serotonin syndrome associated with the use of serotonin and noradrenaline reuptake inhibitors (SNRIs) with serotonin (5-HT_1) agonists such as *sumatriptan* (see p.626).

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Dalcipran; Ixel; ***Austria:*** Dalcipran; Ixel; ***Braz.:*** Ixel; ***Chile:*** Ixel; ***Cz.:*** Dalcipran; Ixel; ***Fin.:*** Ixel; ***Fr.:*** Ixel; ***Israel:*** Ixel; ***Jpn:*** Toledomin; ***Pol.:*** Ixel; ***Port.:*** Dalcipran; Ixel; ***Rus.:*** Ixel (Иксел); ***Turk.:*** Ixel.

Mirtazapine *(BAN, USAN, rINN)*

6-Azamianserin; Mepirzapin; Mepirzepine; Mirtatsapiini; Mirtazapin; Mirtazapina; Mirtazapinum; Org-3770. (*RS*)-1,2,3,4,10,14b-Hexahydro-2-methylpyrazino-[2,1-*a*]pyrido[2,3-*c*][2]benzazepine.

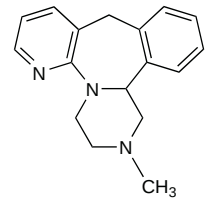
Миртазапин

$C_{17}H_{19}N_3$ = 265.4.

CAS — 61337-67-5.

ATC — N06AX11.

ATC Vet — QN06AX11.



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

Ph. Eur. 6.2 (Mirtazapine). A white or almost white powder, slightly hygroscopic to hygroscopic. It exhibits polymorphism. Practically insoluble in water; freely soluble in anhydrous alcohol. Store in airtight containers.

USP 31 (Mirtazapine). It is anhydrous or contains one-half molecule of water of hydration. A white to creamy white, crystalline powder. Practically insoluble in water; soluble in solvent ether; sparingly soluble in *n*-hexane; freely soluble in methyl alcohol and in toluene. Store in airtight containers.

Adverse Effects

Adverse effects commonly reported with mirtazapine are an increase in appetite and weight, and oedema; drowsiness or sedation generally occur during the first few weeks of treatment. Dizziness, headache, and increases in liver enzyme levels have been reported less commonly; jaundice may occur. Other rarely reported adverse effects include orthostatic hypotension, skin rashes, nightmares, agitation, mania, hallucinations, paraesthesia, convulsions, tremor, myoclonus, psychomotor restlessness including akathisia, restless legs syndrome, arthralgia, myalgia, and reversible agranulocytosis, leucopenia, and granulocytopenia.

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

Incidence of adverse effects. The Australian Adverse Drug Reactions Advisory Committee has reported[1] that, up to October 2003, it had received 253 reports of adverse reactions associated with the use of mirtazapine. The most frequently reported reactions were oedema (33), anxiety or agitation (24), myalgia or arthralgia (24), sedation (23), and skin reactions (20). Other reactions included hyperkinesis, diarrhoea, and nausea and vomiting. There were 16 cases of convulsions, all in patients without a history of epilepsy. Blood dyscrasias were also reported and included 8 cases of neutropenia, 6 of thrombocytopenia, and 1 each of lymphopenia and pancytopenia; in the majority of cases onset was within 2 months of starting mirtazapine.

A prescription-event monitoring study conducted in England identified 13 554 patients who had been prescribed mirtazapine during the first 2 years of marketing in the UK;[2] within this cohort, 807 adverse drug reactions were reported in 573 patients. The most common adverse reactions included drowsiness or sedation (116), malaise (71), dizziness (57), nausea and vomiting (33), weight gain (31), and headache or migraine (21). Facial oedema (5), allergy (3), bone marrow toxicity (2), and myelodysplasia (1) were the more serious suspected adverse reactions.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Convulsions and blood dyscrasias with mirtazapine. *Aust Adverse Drug React Bull* 2003; **22:** 18–19. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0310.pdf (accessed 24/11/05)
2. Biswas PN, *et al*. The pharmacovigilance of mirtazapine: results of a prescription event monitoring study on 13 554 patients in England. *J Psychopharmacol* 2003; **17:** 121–6.

Effects on the endocrine system. An elderly woman developed *hyponatraemia* within 4 days of starting mirtazapine at a dose of 15 mg at night.[1] Apart from her age, other risk factors for hyponatraemia included diuretic use and a previous episode while taking venlafaxine.

1. Roxanas MG. Mirtazapine-induced hyponatraemia. *Med J Aust* 2003; **179:** 453–4.

Effects on mental state. An Expert Working Group was convened in May 2003 by the UK CSM to consider the ongoing safety concerns of the SSRIs particularly the risk of suicidal behaviour in children; the safety of mirtazapine (another serotonergic antidepressant) was also considered. In its final report[1] in December 2004, the group concluded that data from trials received by the CSM had failed to show that mirtazapine was effective in the treatment of depression in **adolescents and children** under 18 years old, although the risk of suicidal behaviour was not increased. Consequently, it was considered that the balance of risks and benefits of mirtazapine for the treatment of depression in this group was unfavourable. Similar recommendations have also been issued in the EU.[2]

The risk of suicide and suicide-related events with serotonergic antidepressant treatment in **adults**, including young adults, are discussed under Fluoxetine, p.392.

1. Weller IVD. *Report of the CSM Expert Working Group on the safety of selective serotonin reuptake inhibitor antidepressants.* London: The Stationery Office, 2005. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON019472&RevisionSelectionMethod=LatestReleased (accessed 14/08/08)
2. European Medicines Agency. European Medicines Agency finalises review of antidepressants in children and adolescents (issued 25th April, 2005). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/12891805en.pdf (accessed 14/08/08)

Effects on the musculoskeletal system. The Netherlands Pharmacovigilance Centre Lareb received 8 reports of arthralgia associated with the use of mirtazapine between May 1995 and October 2004; the effect usually developed within a short time of starting treatment and resolved once the drug was withdrawn.[1] The authors noted that of 4578 reported reactions to mirtazapine held in the WHO database up to March 2004, 110 concerned the development of arthralgia. Similar reactions have occurred with mianserin and nefazodone, and it was suggested that effects at serotonin 5-HT_1 or 5-HT_2 receptors might be involved.

1. Passier A, van Puijenbroek E. Mirtazapine-induced arthralgia. *Br J Clin Pharmacol* 2005; **60:** 570–2.

Extrapyramidal effects. Akathisia that developed in 2 patients given mirtazapine 30 mg at night[1] resolved in one after being treated with clonazepam and in the other patient after reducing the dose of mirtazapine to 15 mg at night.

1. Girishchandra BG, *et al.* Mirtazapine-induced akathisia. *Med J Aust* 2002; **176:** 242.

Serotonin syndrome. The serotonin syndrome (p.416) is most commonly due to the additive adverse effects of two or more drugs that enhance serotonin activity at central receptors; rarely, a single serotonergic drug has caused the syndrome. One such case[1] occurred in an elderly patient given mirtazapine 15 mg daily; he was also taking salbutamol, ipratropium, and nimodipine, although none of these are known to have serotonergic effects.

1. Hernández JL, *et al.* Severe serotonin syndrome induced by mirtazapine monotherapy. *Ann Pharmacother* 2002; **36:** 641–3.

Precautions

Mirtazapine should be used with caution in patients with epilepsy or a history of seizures, and it should be avoided completely if these disorders are unstable. Care is also required in hepatic or renal impairment, and cardiac disorders such as conduction disturbances, angina pectoris, and recent myocardial infarction; caution is further advised in patients with hypotension, diabetes mellitus, psychoses, and in those with a history of bipolar disorder. Treatment should be stopped if jaundice develops. Although mirtazapine has only weak antimuscarinic activity, it should nevertheless be used with care in patients with micturition disturbances, angle-closure glaucoma, and raised intra-ocular pressure.

Because of the risk of bone-marrow depression, patients should be advised to report any of the following symptoms during treatment: fever, sore throat, stomatitis, or other signs of infection; treatment should be stopped and a blood count performed.

Drowsiness is often experienced at the start of therapy and patients, if affected, should not drive or operate machinery.

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.

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

Breast feeding. Mirtazapine has been detected in breast milk;[1] however, the plasma concentration in a breast-fed infant was very low (0.2 nanograms/mL) and no adverse events were detected.

1. Aichhorn W, *et al.* Mirtazapine and breast-feeding. *Am J Psychiatry* 2004; **161:** 2325.

Children. The use of mirtazapine in adolescents and children with depression is not recommended; for further details, see Effects on Mental State, above.

Pregnancy. A small case series followed the pregnancies of 9 women exposed to mirtazapine during the first trimester;[1] in the majority of cases the women were also exposed to other drugs. Within the group there were 7 healthy deliveries, 1 induced abortion, and 1 spontaneous abortion. In another report healthy male twins were delivered by a mother who was given mirtazapine at 2 periods during her pregnancy for the successful treatment of hyperemesis gravidarum.[2] A follow-up examination of the twins at 6 months was normal.

Health Canada has reported that some newborn infants of mothers who took newer antidepressants such as mirtazapine mainly during the third trimester of pregnancy have experienced complications at birth requiring prolonged hospitalisation, breathing support, and tube feeding.[3] Reported symptoms included seizures, muscle rigidity, jitteriness, and constant crying. It was considered that these symptoms represented either direct toxicity of mirtazapine or a possible withdrawal syndrome.

1. Yaris F, *et al.* Newer antidepressants in pregnancy: prospective outcome of a case series. *Reprod Toxicol* 2004; **19:** 235–8.
2. Rohde A, *et al.* Mirtazapine (Remergil) for treatment resistant hyperemesis gravidarum: rescue of a twin pregnancy. *Arch Gynecol Obstet* 2003; **268:** 219–21.
3. Health Canada. Health Canada advises of potential adverse effects of SSRIs and other anti-depressants on newborns (issued 9th August 2004). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2004/2004_44-eng.php (accessed 14/08/08)

Interactions

Mirtazapine should not be used with or within 2 weeks of stopping an MAOI; at least one week should elapse between stopping mirtazapine and starting any drug liable to provoke a serious reaction (e.g. phenelzine). Use of mirtazapine with alcohol or benzodiazepines may potentiate sedative effects.

The cytochrome P450 isoenzyme CYP3A4 is involved in the metabolism of mirtazapine and caution is advised when mirtazapine is given with potent inhibitors of this isoenzyme such as HIV-protease inhibitors, azole antifungals including ketoconazole, erythromycin, and nefazodone; raised plasma levels of mirtazapine have been noted after use with ketoconazole. Conversely, carbamazepine and other inducers of CYP3A4 increased the clearance of mirtazapine and the dose of mirtazapine may need to be increased when given with these drugs.

Cimetidine, which inhibits a range of cytochrome P450 isoenzymes, has more than doubled the bioavailability of mirtazapine; the dose of mirtazapine may need to be reduced if given with cimetidine.

Pharmacokinetics

Mirtazapine is well absorbed from the gastrointestinal tract with peak plasma levels occurring after about 2 hours. Plasma protein binding is about 85%. Mirtazapine is extensively metabolised in the liver and the major biotransformation pathways are demethylation and oxidation followed by glucuronide conjugation; cytochrome P450 isoenzymes involved are CYP2D6, CYP1A2, and CYP3A4. The *N*-desmethyl metabolite is pharmacologically active. Elimination is via urine (75%) and faeces (15%). The mean plasma elimination half-life is 20 to 40 hours. Data from *animal* studies indicate that mirtazapine crosses the placenta. Mirtazapine is distributed into breast milk.

◊ References.

1. Timmer CJ, *et al.* Clinical pharmacokinetics of mirtazapine. *Clin Pharmacokinet* 2000; **38:** 461–74.

Uses and Administration

Mirtazapine, a piperazinoazepine, is an analogue of mianserin (p.408); it is a noradrenergic and specific serotonergic antidepressant. It enhances the release of noradrenaline and, indirectly, serotonin through blockade of central presynaptic adrenergic (α_2) receptors. The effects of released serotonin are mediated via 5-HT_1 receptors as mirtazapine blocks both 5-HT_2 and 5-HT_3 receptors. Mirtazapine is given as a racemic mixture: the *S*(+)-enantiomer blocks α_2 and 5-HT_2 receptors whereas the *R*(−)-enantiomer blocks 5-HT_3 receptors. Mirtazapine is also a potent antagonist at histamine (H_1) receptors which gives it sedative properties; it has very little antimuscarinic activity.

In the treatment of depression (p.373), mirtazapine is given in an initial oral daily dose of 15 mg, which may be increased gradually according to response. Changes in dose should be made at intervals of at least 1 to 2 weeks because of the long half-life. The usual effective daily dose lies within the range of 15 to 45 mg. Daily doses may be given as a single dose, preferably at bedtime, or in 2 equally divided doses. Mirtazapine may also be given by intravenous infusion.

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

Anxiety disorders. Mirtazapine has been tried with some success in the treatment of anxiety disorders (p.952) including obsessive-compulsive disorder (p.952), panic disorder (p.952), and post-traumatic stress disorder (p.953).

References.

1. Boshuisen ML, *et al.* The effect of mirtazapine in panic disorder: an open label pilot study with a single-blind placebo run-in period. *Int Clin Psychopharmacol* 2001; **16:** 363–8.
2. Davidson JR, *et al.* Mirtazapine vs placebo in posttraumatic stress disorder: a pilot trial. *Biol Psychiatry* 2003; **53:** 188–91.
3. Chung MY, *et al.* Efficacy and tolerability of mirtazapine and sertraline in Korean veterans with posttraumatic stress disorder: a randomized open label trial. *Hum Psychopharmacol* 2004; **19:** 489–94.
4. Koran LM, *et al.* Mirtazapine for obsessive-compulsive disorder: an open trial followed by double-blind discontinuation. *J Clin Psychiatry* 2005; **66:** 515–20.

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. Mirtazapine is a central presynaptic adrenergic (α_2) receptor antagonist and has a slightly different biochemical profile from both the tricyclics and the SSRIs; however, like the SSRIs, mirtazapine appears to have fewer unpleasant adverse effects in comparison with the older tricyclics.

References.

1. Kasper S, *et al.* A risk-benefit assessment of mirtazapine in the treatment of depression. *Drug Safety* 1997; **17:** 251–64.
2. Montgomery SA, *et al.* Mirtazapine versus amitriptyline in the long-term treatment of depression: a double-blind placebo-controlled study. *Int Clin Psychopharmacol* 1998; **13:** 63–73.
3. Puzantian T. Mirtazapine, an antidepressant. *Am J Health-Syst Pharm* 1998; **55:** 44–9.
4. Holm KJ, Markham A. Mirtazapine: a review of its use in major depression. *Drugs* 1999; **57:** 607–31.
5. Schatzberg AF, *et al.* Double-blind, randomized comparison of mirtazapine and paroxetine in elderly depressed patients. *Am J Geriatr Psychiatry* 2002; **10:** 541–50.
6. Wade A, *et al.* A randomized, double-blind, 24-week study comparing the efficacy and tolerability of mirtazapine and paroxetine in depressed patients in primary care. *Int Clin Psychopharmacol* 2003; **18:** 133–41.
7. Versiani M, *et al.* Comparison of the effects of mirtazapine and fluoxetine in severely depressed patients. *CNS Drugs* 2005; **19:** 137–46.

Nausea and vomiting. Mirtazapine has been investigated in the management of severe nausea and vomiting (p.1700). For mention of the successful use of mirtazapine to treat hyperemesis of pregnancy see Pregnancy, under Precautions, above.

Further references.

1. Kast RE. Mirtazapine may be useful in treating nausea and insomnia of cancer chemotherapy. *Support Care Cancer* 2001; **9:** 469–70.
2. Caldis EV, Gair RD. Mirtazapine for treatment of nausea induced by selective serotonin reuptake inhibitors. *Can J Psychiatry* 2004; **49:** 707.
3. Teixeira FV, *et al.* Mirtazapine (Remeron) as treatment for non-mechanical vomiting after gastric bypass. *Obes Surg* 2005; **15:** 707–9.

Preparations

USP 31: Mirtazapine Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Comenter; Noxibel; Remeron; ***Austral.:*** Avanza; Axit; Mirtazon; Remeron; ***Austria:*** Lanazapin; Mirtabene; Mirtaron; Mirtel; Remeron; ***Belg.:*** Remergon; ***Braz.:*** Remeron; ***Canad.:*** Remeron; ***Chile:*** Amirel; Ciblex; Divaril; Promyrtil; Zuleptan; ***Cz.:*** Calixta; Esprital; Mirtastad; Mirzaten; Remeron; Valdren; ***Denm.:*** Arintapin; Combar; Mirtazon; Remeron; ***Fin.:*** Mirtaril; Mirtazon; Remeron; ***Fr.:*** Norset; ***Ger.:*** Mirta TAD; MirtaLich; Mirtazelon; Mirtazza; Remergil; ***Gr.:*** Azapin; Depreram; Remeron; ***Hong Kong:*** Remeron; ***Hung.:*** Mirtadepi; Mirtel; Mirzaten; Mizapin; Remeron; ***India:*** Mirtaz; ***Indon.:*** Remeron; ***Irl.:*** Mirap; Tazamel; Zismirt; Zispin; ***Israel:*** Miro; Remeron; ***Ital.:*** Remeron; ***Malaysia:*** Remeron; ***Mex.:*** Comenter; Mirzalux; Remeron; ***Neth.:*** Remeron; ***Norw.:*** Remeron; ***NZ:*** Remeron; ***Philipp.:*** Remeron; ***Pol.:*** Esprital; Mirtastad; Mirzaten; Remeron; ***Port.:*** Mirtazon; Remeron; ***Rus.:*** Mirzaten (Мирзатен); Remeron (Ремерон)†; ***S.Afr.:*** Remeron; ***Singapore:*** Remeron; ***Spain:*** Afloyan; Rexer; Vastat; ***Swed.:*** Remeron; ***Switz.:*** Remeron; ***Thai.:*** Remeron; ***Turk.:*** Remeron; ***UK:*** Zispin; ***USA:*** Remeron; ***Venez.:*** Comenter; Remeron.

Moclobemide *(BAN, USAN, rINN)*

Moclobemida; Moclobémide; Moclobemidum; Moklobemid; Moklobemidi; Ro-11-1163; Ro-11-1163/000. 4-Chloro-*N*-(2-morpholinoethyl)benzamide.

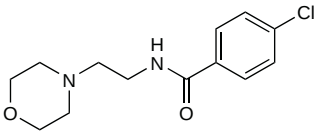
Моклобемид

$C_{13}H_{17}ClN_2O_2$ = 268.7.

CAS — 71320-77-9.

ATC — N06AG02.

ATC Vet — QN06AG02.



Pharmacopoeias. In *Chin.* and *Swiss*.

Adverse Effects

Adverse effects reported to occur with moclobemide include sleep disturbances, dizziness, agitation, feelings of anxiety, restlessness, irritability, and headache. Gastrointestinal disturbances include dry mouth, diarrhoea, constipation, and nausea and vomiting. Paraesthesia, visual disturbances, and oedema have also been reported, and skin reactions include rash, pruritus, urticaria, and flushing. Confusional states have been observed that disappear rapidly on stopping the drug. Raised liver enzymes and galactorrhoea have been reported rarely.

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

Effects on the cardiovascular system. Hypertension has been reported[1,2] rarely in patients taking moclobemide, some of whom were also taking other drugs although moclobemide was suspected to be the cause. Blood pressure usually returned to normal after stopping moclobemide.

1. Coulter DM, Pillans PI. Hypertension with moclobemide. *Lancet* 1995; **346:** 1032.
2. Boyd IW. Hypertension with moclobemide. *Lancet* 1995; **346:** 1498.

Effects on the endocrine system. A prescription-event monitoring study found that galactorrhoea is significantly associated with the use of moclobemide.[1]

1. Dunn NR, *et al.* Galactorrhoea with moclobemide. *Lancet* 1998; **351:** 802.

Effects on the liver. An 85-year-old woman developed intrahepatic cholestasis after taking moclobemide for about 1 week;[1] she had previously been taking fluoxetine and was switched to moclobemide without a washout period. She died 12 days after the onset of jaundice despite prompt moclobemide withdrawal.

1. Timmings P, Lamont D. Intrahepatic cholestasis associated with moclobemide leading to death. *Lancet* 1996; **347:** 762–3.

Overdosage. Several case series[1-3] have suggested that moclobemide is relatively safe when taken alone in overdose; symptoms such as gastrointestinal irritation, agitation, aggression, behavioural disturbances, and tachycardia have been noted. However, fatalities have been reported, particularly when taken with other serotonergic drugs.[3,4]

1. Hetzel W. Safety of moclobemide taken in overdose for attempted suicide. *Psychopharmacology (Berl)* 1992; **106:** S127–S129.
2. Myrenfors PG, *et al.* Moclobemide overdose. *J Intern Med* 1993; **233:** 113–15.
3. Isbister GK, *et al.* Moclobemide poisoning: toxicokinetics and occurrence of serotonin toxicity. *Br J Clin Pharmacol* 2003; **56:** 441–50.
4. Giroud C, *et al.* Death following acute poisoning by moclobemide. *Forensic Sci Int* 2004; **140:** 101–7.

Precautions

Moclobemide is contra-indicated in patients with acute confusional states and in those with phaeochromocytoma. It should be avoided in excited or agitated patients, unless used with a sedative. Manic episodes may be provoked in patients with bipolar disorder. Care is also required in patients with thyrotoxicosis as moclobemide may theoretically precipitate a hypertensive reaction. Reduced doses should be used in patients with severe hepatic impairment.

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.

Although impairment of mental alertness is generally not expected with moclobemide, caution should be exercised with respect to driving or operating machinery until individual reactions have been assessed.

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

Breast feeding. In a study[1] of the distribution of moclobemide into the breast milk of 6 mothers given a single 300-mg dose of moclobemide, a mean of 0.057% of the dose appeared in breast milk as moclobemide and 0.031% as Ro-12-8095, its major metabolite, within 24 hours of a dose. It was considered that this small amount of moclobemide was unlikely to be hazardous to breast-fed infants. UK licensed drug information advises caution and consideration of the benefits of moclobemide therapy to the mother against possible risks to the infant.

1. Pons G, *et al.* Moclobemide excretion in human breast milk. *Br J Clin Pharmacol* 1990; **29:** 27–31.

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

Pregnancy. UK licensed drug information recommends that moclobemide should only be used during pregnancy if the benefits to the mother outweigh any possible risks to the fetus.

A patient who took at least 300 mg daily of moclobemide throughout her pregnancy delivered a healthy, full-term infant after an uncomplicated pregnancy.[1] The infant was monitored from birth, and psychomotor and somatic development for the first 14 months was found to be normal.

1. Rybakowski JK. Moclobemide in pregnancy. *Pharmacopsychiatry* 2001; **34:** 82–3.

Withdrawal. Withdrawal symptoms may occur if an antidepressant such as moclobemide is suddenly stopped after regular use for 8 weeks or more; the *BNF* recommends that the dose should be tapered gradually over a period of about 4 weeks, or as much as 6 months in patients who have been receiving long-term maintenance therapy.

Despite reducing the dose of moclobemide over 3 days, symptoms such as muscle cramps, shivering, headache, nausea, and hot flushes developed in a 47-year-old woman on the day that moclobemide was completely stopped.[1] The patient had been taking moclobemide for about 15 months.

1. Curtin F, *et al.* Moclobemide discontinuation syndrome predominantly presenting with influenza-like symptoms. *J Psychopharmacol* 2002; **16:** 271–2.

Interactions

The dietary restrictions that need to be followed with selective reversible inhibitors of monoamine oxidase type A such as moclobemide are less stringent than those for non-selective inhibitors of monoamine oxidase types A and B (see under Interactions of Phenelzine, p.417). However, UK licensed drug information recommends that since some patients may be especially sensitive to tyramine, consumption of large amounts of tyramine-rich food should be avoided.

Medicines containing *sympathomimetics*, *dextromethorphan*, or *anorectics* should not be taken with moclobemide. Moclobemide should not be given with *other antidepressants* although, owing to its short duration of action, a treatment-free period is generally considered unnecessary after its cessation. For further details, see Antidepressants under Interactions of Phenelzine, p.418. Therapy with moclobemide should not be started until at least a week after cessation of a tricyclic or related antidepressant or an SSRI or related antidepressant (2 weeks in the case of paroxetine and sertraline; at least 5 weeks in the case of fluoxetine) or for at least a week after stopping treatment with non-selective MAOIs. CNS excitation or depression may occur if moclobemide is taken with *opioid analgesics*, and there is also a risk of CNS toxicity if taken with *serotonin (5-HT$_1$) agonists*. The metabolism of moclobemide is inhibited by *cimetidine*, leading to increased plasma concentrations and a need for reduced dosage (see below).

Antimigraine drugs. For the effects of moclobemide on *serotonin (5-HT$_1$) agonists*, see under Sumatriptan, p.626.

Cimetidine. Cimetidine 1 g daily for 2 weeks increased the mean maximum plasma concentration of moclobemide in 8 healthy subjects from 575 nanograms/mL to 787 nanograms/mL; several other parameters associated with moclobemide absorption and disposition were also affected.[1] It was suggested that a reduction in the dosage of moclobemide might be required. UK licensed drug information for moclobemide recommends reducing its dose by half in patients also receiving cimetidine.

1. Schoerlin M-P, *et al.* Cimetidine alters the disposition kinetics of the monoamine oxidase-A inhibitor moclobemide. *Clin Pharmacol Ther* 1991; **49:** 32–8.

Dopaminergics. Adverse effects including nausea, vomiting, and dizziness were noted in healthy subjects given moclobemide and *levodopa with benserazide*;[1] however, no significant hypertensive reactions were seen.

Caution is also required when *selegiline* and moclobemide are given together.[1] Dietary restrictions with this combination (see under Phenelzine, p.417) are recommended by one manufacturer of selegiline, whereas another advises that this combination should be avoided (as does the manufacturer of moclobemide).

See also under Selegiline, p.817.

1. Dingemanse J. An update of recent moclobemide interaction data. *Int Clin Psychopharmacol* 1993; **7:** 167–80.

Omeprazole. Omeprazole, which is an inhibitor of cytochrome P450 isoenzyme CYP2C19, increased plasma concentrations and elimination half-life of moclobemide in extensive metabolisers of the drug towards values seen in poor metabolisers.[1] It had little effect on pharmacokinetic parameters in poor metabolisers. The clinical effects were uncertain but extra care might be warranted if the 2 drugs are given together.

1. Yu K-S, *et al.* Effect of omeprazole on the pharmacokinetics of moclobemide according to the genetic polymorphism of CYP2C19. *Clin Pharmacol Ther* 2001; **69:** 266–73.

Opioid analgesics. Symptoms suggestive of a mild serotonin syndrome (p.416) developed in a 73-year-old woman taking moclobemide, nortriptyline, and lithium after she was given *pethidine* intravenously.[1] Licensed drug information recommends that moclobemide should not be given with pethidine.

1. Gillman PK. Possible serotonin syndrome with moclobemide and pethidine. *Med J Aust* 1995; **162:** 554.

Pharmacokinetics

Moclobemide is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring within about 1 hour of ingestion. Absorption is virtually complete but first-pass metabolism reduces bioavailability of the drug. Moclobemide is widely distributed throughout the body and is 50% bound to plasma proteins. It undergoes extensive metabolism in the liver, in part by the cytochrome P450 isoenzymes CYP2C19 and CYP2D6. Metabolites of moclobemide and a small amount of unchanged drug are excreted in the urine. Moclobemide has a plasma elimination half-life of 2 to 4 hours. Moclobemide is distributed into breast milk.

◊ References.

1. Mayersohn M, Guentert TW. Clinical pharmacokinetics of the monoamide oxidase-A inhibitor moclobemide. *Clin Pharmacokinet* 1995; **29:** 292–332.
2. Gram LF, *et al.* Moclobemide: a substrate of CYP2C19 and an inhibitor of CYP2C19, CYP2D6, and CYP1A2: a panel study. *Clin Pharmacol Ther* 1995; **57:** 670–7.

Uses and Administration

Moclobemide, a benzamide derivative, is a reversible inhibitor of monoamine oxidase type A (RIMA) (see under Phenelzine, p.419) used for the treatment of depression and of social anxiety disorder.

In the treatment of **depression** the usual initial oral dose of moclobemide is 300 mg daily in divided doses. This may be increased up to 600 mg daily according to response. In some patients, a maintenance dose of 150 mg daily may be sufficient.

In the treatment of **social anxiety disorder**, the initial daily dose of moclobemide is 300 mg increased after 3 days to 600 mg given in 2 divided doses. Treatment should be continued for 8 to 12 weeks to assess efficacy; patients should be periodically re-evaluated thereafter to determine the need for further treatment.

Moclobemide should be taken after food.

Reduced doses should be given in hepatic impairment (see below) and in patients also taking cimetidine (see above).