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.

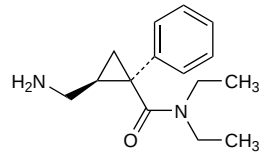
Мильнаципрана Гидрохлорид

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

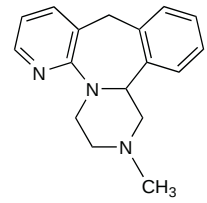
Миртазапин

$C_{17}H_{19}N_3$ = 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]