Preparations

USP 31: Maprotiline Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Austria: Ludiomil; ***Belg.:*** Ludiomil; ***Braz.:*** Ludiomil; ***Canad.:*** Ludiomil†; ***Chile:*** Mapromil; ***Cz.:*** Ludiomil; Maprotibene; ***Denm.:*** Ludiomil; Maludil; ***Fr.:*** Ludiomil; ***Ger.:*** Deprilept; Ludiomil; Maprolu; ***Gr.:*** Aprotilin†; Ludiomil; ***Hong Kong:*** Ludiomil†; ***Hung.:*** Ludiomil; Maprolu†; ***Indon.:*** Ludiomil; Ludios; Sandepril; Tilsan; ***Israel:*** Melodil; ***Ital.:*** Ludiomil; ***Malaysia:*** Ludiomil; ***Mex.:*** Ludiomil; ***Neth.:*** Ludiomil; ***NZ:*** Ludiomil; ***Pol.:*** Ludiomil; ***Port.:*** Ludiomil; ***Rus.:*** Ludiomil (Людиомил); ***S.Afr.:*** Ludiomil; ***Singapore:*** Ludiomil†; ***Spain:*** Ludiomil; ***Swed.:*** Ludiomil; ***Switz.:*** Ludiomil; ***Thai.:*** Ludiomil; ***Turk.:*** Ludiomil; Maprotil; ***UK:*** Ludiomil†; ***Venez.:*** Ludiomil.

Melitracen Hydrochloride *(USAN, rINNM)*

Hidrocloruro de melitraceno; Mélitracène, Chlorhydrate de; Melitraceni Hydrochloridum; N-7001; U-24973A. 3-(9,10-Dihydro-10,10-dimethyl-9-anthrylidene)propyldimethylamine hydrochloride.

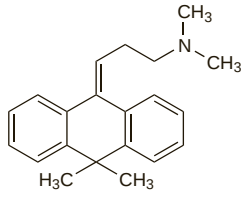
Мелитрацена Гидрохлорид

$C_{21}H_{25}N,HCl$ = 327.9.

CAS — 5118-29-6 (melitracen); 10563-70-9 (melitracen hydrochloride).

ATC — N06AA14.

ATC Vet — QN06AA14.



(melitracen)

Profile

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

In the treatment of depression (p.373) melitracen is given orally as the hydrochloride although doses are expressed in terms of the base; melitracen hydrochloride 28.1 mg is equivalent to about 25 mg of melitracen. The recommended initial dose is the equivalent of 25 mg two or three times daily gradually increased to a total of 225 mg daily if necessary. Elderly patients should generally be given reduced doses of 25 or 30 mg daily initially. Melitracen may also be given in lower doses with flupentixol (p.997) in the management of depression with anxiety. A combination of melitracen 10 mg and flupentixol 500 micrograms is given orally in the morning and at midday. In severe cases the morning dose may be doubled. The total daily dose should not exceed melitracen 40 mg and flupentixol 2 mg. Elderly patients may be given melitracen 10 mg with flupentixol 500 micrograms in the morning; in severe cases this dose may be given in the morning and at midday.

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

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Dixeran; ***Belg.:*** Dixeran†.

Multi-ingredient: ***Austria:*** Deanxit; ***Belg.:*** Deanxit; ***Hong Kong:*** Anfree; Deanxit; ***Ital.:*** Deanxit†; ***Singapore:*** Deanxit; ***Spain:*** Deanxit; ***Switz.:*** Deanxit; ***Thai.:*** Deanxit.

Mianserin Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de mianserina; Mianseriinihydrokloridi; Mianserin Hidroklorür; Miansérine, chlorhydrate de; Mianserin-hydrochlorid; Mianserinhydroklorid; Mianserini hydrochloridum; Mianserino hidrochloridas; Mianseryny chlorowodorek; Mianszerin-hidroklorid; Org-GB-94. 1,2,3,4,10,14b-Hexahydro-2-methyldibenzo[*c,f*]pyrazino[1,2-*a*]azepine hydrochloride.

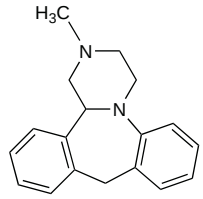
Миансерина Гидрохлорид

$C_{18}H_{20}N_2,HCl$ = 300.8.

CAS — 24219-97-4 (mianserin); 21535-47-7 (mianserin hydrochloride).

ATC — N06AX03.

ATC Vet — QN06AX03.



(mianserin)

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

Ph. Eur. 6.2 (Mianserin Hydrochloride). A white or almost white crystalline powder or crystals. Sparingly soluble in water; slightly soluble in alcohol; soluble in dichloromethane. A 1% solution in water has a pH of 4.0 to 5.5. Protect from light.

Adverse Effects

Antimuscarinic and cardiac adverse effects are fewer and milder with mianserin, a tetracyclic antidepressant, than with tricyclic antidepressants but effects are otherwise broadly similar (see Amitriptyline, p.376); mianserin may be associated with a lower risk of cardiotoxicity in overdosage.

The most common adverse effect associated with mianserin is drowsiness. Mianserin also causes bone-marrow depression usually presenting as leucopenia, granulocytopenia, or agranulocytosis; aplastic anaemia has been reported. These adverse haematological reactions generally occur during the first few weeks of therapy and especially in the elderly.

Other adverse effects reported include disturbances of liver function and jaundice, breast disorders (gynaecomastia, nipple tenderness, and non-puerperal lactation), and polyarthropathy.

Effects on the blood. Between 1976 and the end of 1988 the UK CSM had received 239 reports of adverse haematological reactions associated with mianserin use.[1] The reports included 68 of agranulocytosis and 84 of granulocytopenia or leucopenia where mianserin was considered to be the probable or possible cause; there had been 17 fatalities. Allowing for the pattern of prescribing there was a greater number of reports of white blood cell disorders in patients over 65 years of age but there was no sex difference. The data also indicated that the adverse reactions were most likely to develop during the first 3 months of therapy. By the end of 1992 the number of reports of mianserin-induced agranulocytosis or neutropenia received by the CSM[2] had risen to 79 and 105, respectively.

A case of fatal aplastic anaemia associated with mianserin use has also been reported.[3]

Proposed mechanisms of mianserin haematotoxicity have included a direct toxicity[4] and an immunologically-mediated mechanism.[5] There is evidence from studies *in vitro* of a significant correlation between the desmethyl metabolite and cytotoxicity. Mianserin is given as a racemic preparation and the formation of metabolites was greater with the *R*(−)-enantiomer than with the *S*(+)-enantiomer.[6]

1. CSM. Mianserin and white blood cell disorders in the elderly. *Current Problems 25* 1989. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024441&RevisionSelectionMethod=LatestReleased (accessed 05/08/08)
2. CSM/MCA. Drug-induced neutropenia and agranulocytosis. *Current Problems* 1993; **19:** 10–11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024456&RevisionSelectionMethod=LatestReleased (accessed 05/08/08)
3. Durrant S, Read D. Fatal aplastic anaemia associated with mianserin. *BMJ* 1982; **285:** 437.
4. O'Donnell JL, *et al.* Possible mechanism for mianserin induced neutropenia associated with saturable elimination kinetics. *BMJ* 1985; **291:** 1375–6.
5. Stricker BHC, *et al.* Thrombocytopenia and leucopenia with mianserin-dependent antibodies. *Br J Clin Pharmacol* 1985; **19:** 102–4.
6. Riley RJ, *et al.* A stereochemical investigation of the cytotoxicity of mianserin metabolites in vitro. *Br J Clin Pharmacol* 1989; **27:** 823–30.

Effects on the cardiovascular system. Although mianserin is considered to be less cardiotoxic than the tricyclic antidepressants adverse effects have been noted in individual patients. Two elderly patients developed signs of disturbed cardiac function (cardiac failure, atrial and ventricular fibrillation, bradycardia, and frequent ventricular ectopic beats) which resolved after the drug was stopped.[1] One of the patients also developed hypokalaemia which was possibly caused by mianserin. It was suggested that persons most likely to experience problems were the elderly with a history of cardiovascular disorders. Further reports of mianserin-induced cardiac effects include recurrent ventricular fibrillation in a 61-year-old man after an overdose of mianserin[2] and bradycardia in a 50-year-old woman after a therapeutic dose.[3]

1. Whiteford H, *et al.* Disturbed cardiac function possibly associated with mianserin therapy. *Med J Aust* 1984; **140:** 166–7.
2. Haefeli WE, *et al.* Recurrent ventricular fibrillation in mianserin intoxication. *BMJ* 1991; **302:** 415–16.
3. Carcone B, *et al.* Symptomatic bradycardia caused by mianserin at therapeutic doses. *Hum Exp Toxicol* 1991; **10:** 383–4.

Effects on the liver. By March 1985 the UK CSM had received 57 reports of hepatic reactions associated with mianserin use from a total of 5 million prescriptions. Reactions had included jaundice and other abnormalities of liver function, but no fatalities had been reported.[1]

Case reports have also been published concerning jaundice;[2-5] liver function returned to normal after stopping mianserin or lowering the dose.

1. CSM. Dangers of newer antidepressants. *Current Problems 15* 1985. http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024422&RevisionSelectionMethod=LatestReleased (accessed 14/08/08)
2. Adverse Drug Reactions Advisory Committee. Mianserin: a possible cause of neutropenia and agranulocytosis. *Med J Aust* 1980; **2:** 673–4.
3. Goldstraw PW, *et al.* Mianserin and jaundice. *N Z Med J* 1983; **96:** 985.
4. Zarski J-P, *et al.* Toxicité hépatique des nouveaux anti-dépresseurs: a propos d'une observation. *Gastroenterol Clin Biol* 1983; **7:** 220–1.
5. Otani K, *et al.* Hepatic injury caused by mianserin. *BMJ* 1989; **299:** 519.

Effects on the musculoskeletal system. A patient developed an acute polyarthritis affecting the hands and feet 6 days after starting therapy with mianserin;[1] at that time the UK CSM had received 19 reports of arthritis and arthralgia associated with mianserin. For the suggestion that effects at serotonin receptors may be involved in such adverse effects see under Mirtazapine, p.410.

1. Hughes A, Coote J. Arthropathy associated with treatment with mianserin. *BMJ* 1986; **292:** 1050.

Effects on the skin. Reports of adverse dermatological reactions in individual patients related to mianserin therapy have included toxic epidermal necrolysis[1] and erythema multiforme.[2,3]

1. Randell P. Tolvon and toxic epidermal necrolysis. *Med J Aust* 1979; **2:** 653.
2. Quraishy E. Erythema multiforme during treatment with mianserin—a case report. *Br J Dermatol* 1981; **104:** 481.
3. Cox NH. Erythema multiforme due to mianserin—a case against generic prescribing. *Br J Clin Pract* 1985; **39:** 293–4.

Effects on the tongue. Glossitis associated with mianserin therapy was reported in 2 patients.[1] Additionally, glossitis accompanied by severe facial oedema has been noted in another patient.[2] In all cases symptoms resolved after withdrawal of mianserin.

1. de la Fuente JR, Berlanga C. Glossitis associated with mianserin. *Lancet* 1984; **i:** 233.
2. Leibovitch G, *et al.* Severe facial oedema and glossitis associated with mianserin. *Lancet* 1989; **ii:** 871–2.

Epileptogenic effect. By March 1985 the UK CSM had received 64 reports of convulsions associated with mianserin use from a total of 5 million prescriptions.[1] In a previous review[2] concerning 40 of these cases it was considered that a causal connection could be established only in a minority. It was suggested that mianserin is no more epileptogenic than tricyclic antidepressants, an opinion that was also shared by other reviewers.[3]

1. CSM. Dangers of newer antidepressants. *Current Problems 15* 1985. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024422&RevisionSelectionMethod=LatestReleased (accessed 05/08/08)
2. Edwards JG, Glen-Bott M. Mianserin and convulsive seizures. *Br J Clin Pharmacol* 1983; **15:** 299S–311S.
3. Richens A, *et al.* Antidepressant drugs, convulsions and epilepsy. *Br J Clin Pharmacol* 1983; **15:** 295S–298S.

Overdosage. Experience with 100 consecutive cases of intoxication with mianserin[1] revealed that when it was the only drug ingested symptoms were mild and neither deep coma nor convulsions occurred. More serious symptoms and 2 fatalities were seen in patients who had taken multiple drug overdoses. The results suggested that after an acute overdose mianserin is less toxic than the tricyclic antidepressants. This conclusion was also supported by a large follow-up study[2] comparing the outcome of suicide attempts among patients who had taken mianserin in overdose with those who had taken amitriptyline.

1. Chand S, *et al.* One hundred cases of acute intoxication with mianserin hydrochloride. *Pharmakopsychiatrie* 1981; **14:** 15–17.
2. Inman WHW. Blood disorders and suicide in patients taking mianserin or amitriptyline. *Lancet* 1988; **ii:** 90–2.

Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p.378). Although mianserin is less cardiotoxic than the tricyclic antidepressants, it still should be used with caution in patients with cardiovascular disorders, such as heart block, or after recent myocardial infarction. Similarly, patients with angle-closure glaucoma or prostatic hyperplasia should be monitored even though antimuscarinic effects are rare. Mianserin should be used with caution in patients with diabetes mellitus, epilepsy, and hepatic or renal impairment; it should be avoided in severe hepatic disease.

Patients should be carefully 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.

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.

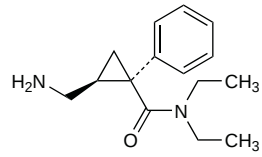
Мильнаципрана Гидрохлорид

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

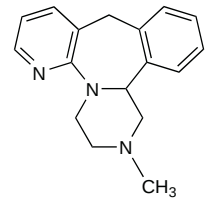
Миртазапин

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