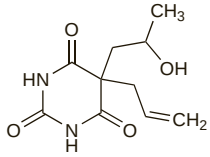
Proxibarbal *(rINN)*

HH-184; Proksybarbal; Proxibarbalum; Proxibarbital. 5-Allyl-5-(2-hydroxypropyl)barbituric acid.

Проксибарбал

$C_{10}H_{14}N_2O_4$ = 226.2.
CAS — 2537-29-3.
ATC — N05CA22.
ATC Vet — QN05CA22.



Pharmacopoeias. In *Pol.*

Profile
Proxibarbal is a barbiturate with general properties similar to those of amobarbital (p.961). It has been used as a sedative in the management of anxiety disorders. It has also been used in the treatment of headache. However, barbiturates are not considered appropriate in the management of these conditions. Proxibarbal has been associated with severe hypersensitivity-induced thrombocytopenia.

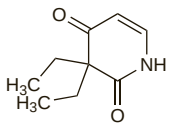
Preparations
Proprietary Preparations (details are given in Part 3)
Hung.: Vasalgin.

Pyrithyldione *(rINN)*

Didropyridinum; NU-903; Piritildiona; Pyrithyldionum; Pyrityldion; Pyrityylidioni. 3,3-Diethylpyridine-2,4(1*H*,3*H*)-dione.

Пиритильдион

$C_9H_{13}NO_2$ = 167.2.
CAS — 77-04-3.
ATC — N05CE03.
ATC Vet — QN05CE03.



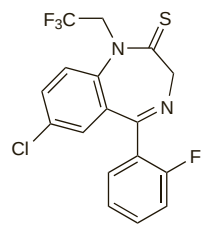
Profile
Pyrithyldione has been given in preparations with diphenhydramine in the short-term management of insomnia but there have been reports of agranulocytosis associated with the use of this combination.

Quazepam *(BAN, USAN, rINN)*

Kvatsepaami; Kvazepam; Quazépam; Quazepamum; Sch-16134. 7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-1-(2,2,2-trifluoroethyl)-1,4-benzodiazepine-2-thione.

Квазепам

$C_{17}H_{11}ClF_4N_2S$ = 386.8.
CAS — 36735-22-5.
ATC — N05CD10.
ATC Vet — QN05CD10.



Pharmacopoeias. In *US.*
USP 31 (Quazepam). Off-white to yellowish powder.

Dependence and Withdrawal
As for Diazepam, p.987.

Adverse Effects, Treatment, and Precautions
As for Diazepam, p.987.

Breast feeding. The American Academy of Pediatrics[1] considers that, although the effect of quazepam on breast-fed infants is unknown, its use by mothers during breast feeding may be of concern since psychotropic drugs do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

However, a study in 4 women given a single 15-mg dose of quazepam found that only about 0.1% of the dose was excreted over 48 hours in breast milk, as quazepam and its 2 major metabolites.[2]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)
2. Hilbert JM, *et al.* Excretion of quazepam into human breast milk. *J Clin Pharmacol* 1984; **24:** 457–62.

Interactions
As for Diazepam, p.989.

Pharmacokinetics
Quazepam is readily absorbed from the gastrointestinal tract after oral doses, peak plasma concentrations being reached in about 2 hours. It is metabolised extensively in the liver. The principal active metabolites are 2-oxoquazepam and *N*-desalkyl-2-oxoquazepam (*N*-desalkylflurazepam) which have elimination half-lives of about 39 and 73 hours respectively, compared with a half-life of 39 hours for quazepam. Further hydroxylation occurs and quazepam is excreted in urine and faeces mainly as conjugated metabolites.

Quazepam and its two active metabolites are more than 95% bound to plasma proteins. Quazepam and its metabolites are distributed into breast milk.

Uses and Administration
Quazepam is a long-acting benzodiazepine with general properties similar to those of diazepam (p.992). It is given as a hypnotic in the short-term management of insomnia (p.957), in an initial oral dose of 15 mg at night; in elderly or debilitated patients and some other patients this can be reduced to 7.5 mg.

Preparations
USP 31: Quazepam Tablets.

Proprietary Preparations (details are given in Part 3)
Ital.: Quazium†; ***Jpn:*** Doral; ***Port.:*** Prosedar†; ***S.Afr.:*** Dorme†; ***Spain:*** Quiedorm; ***USA:*** Doral.

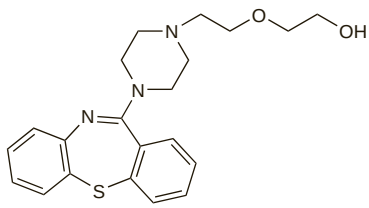
Quetiapine Fumarate

(BANM, USAN, pINNM)

Fumarato de quetiapina; ICI-204636; Quétiapine, Fumarate de; Quetiapini Fumaras; ZD-5077; ZM-204636. 2-[2-(4-Dibenzo[*b*,*f*][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]ethanol fumarate (2:1) salt.

Кветиапина Фумарат

$(C_{21}H_{25}N_3O_2S)_2, C_4H_4O_4$ = 883.1.
CAS — 111974-69-7 (quetiapine); 111974-72-2 (quetiapine fumarate).
ATC — N05AH04.
ATC Vet — QN05AH04.



(quetiapine)

Adverse Effects, Treatment, and Precautions
Although quetiapine may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p.969), the incidence and severity of such effects may vary. Quetiapine has been associated with a low incidence of extrapyramidal symptoms but tardive dyskinesia may occur after long-term treatment. Rises in prolactin concentrations may be less than with chlorpromazine.

The most frequent adverse effects with quetiapine are somnolence and dizziness. Mild asthenia, anxiety, fever, rhinitis, peripheral oedema, constipation, dyspepsia, dry mouth, and raised liver enzyme values are also relatively common. Orthostatic hypotension associated with dizziness, tachycardia, and syncope has been reported, particularly during initial dose-titration. Prolongation of QT interval is rarely significant with quetiapine. Hyperglycaemia and exacerbation of pre-existing diabetes have been reported rarely. Clinical monitoring for hyperglycaemia has been recommended, especially in patients with, or at risk of developing, diabetes. Weight gain, particularly during early treatment, has also been noted. Neuroleptic malignant syndrome is rare with quetiapine. Leucopenia, neutropenia, and eosinophilia have also been reported. Other adverse effects have included rises in plasma-triglyceride and cholesterol concentrations, and reduced plasma-thyroid hormone concentrations. There have been rare reports of seizures, hypersensitivity reactions including angioedema, and priapism.

Asymptomatic changes in the lens of the eye have occurred in patients during long-term treatment with quetiapine; cataracts have developed in *dogs* during chronic dosing studies. In the USA, it is recommended that patients should have an eye examination to detect cataract formation when starting therapy with quetiapine and every 6 months during treatment.

Quetiapine should be used with caution in patients with hepatic or renal impairment, with cardiovascular disease or other conditions predisposing to hypotension, with cerebrovascular disease, or with a history of seizures or conditions that lower the seizure threshold.

When quetiapine is used for the depressive phase in bipolar disorder, 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 Bipolar Disorder, p.372.

Quetiapine may affect the performance of skilled tasks including driving.

Gradual withdrawal of quetiapine is recommended because of the risk of withdrawal symptoms, including nausea, vomiting, insomnia, and rebound psychoses, with abrupt cessation.

Breast feeding. In a case report[1] of a mother receiving quetiapine 200 mg daily by mouth, the maximum concentration of the drug in breast milk an hour after the dose was reported to be 62 micrograms/litre; the mean concentration over 6 hours was 13 micrograms/litre. The authors concluded that the breast-fed infant would ingest, at maximum, the daily equivalent of 0.43% of the weight-adjusted maternal dose. Follow-up at 4.5 months reported no adverse effects in the infant, who had been breast fed from 8 weeks of age.

Licensed product information recommends that patients receiving quetiapine should not breast feed.

1. Lee A, *et al.* Excretion of quetiapine in breast milk. *Am J Psychiatry* 2004; **161:** 1715–16.

Dementia. The FDA[1] has issued advice against the use of atypical antipsychotics in the treatment of behavioural problems in elderly patients with dementia after analysis of placebo-controlled studies showed an increased risk of mortality with certain drugs of this class, including quetiapine; most of the deaths appeared due to cardiovascular events or infection. See also under Risperidone, p.1024.

1. FDA. FDA issues public health advisory for antipsychotic drugs used for treatment of behavioral disorders in elderly patients (issued 11th April, 2005). Available at: http://www.fda.gov/bbs/topics/ANSWERS/2005/ANS01350.html (accessed 30/05/05)

Effects on the blood. There have been reports of leucopenia,[1] neutropenia,[2] and pancytopenia[3] associated with quetiapine therapy; all 3 patients improved when the drug was stopped. Thrombotic thrombocytopenic purpura has also been reported in a patient who received quetiapine on 2 separate occasions 2 years apart.[4] From December 1997 to October 2006, Health Canada[5] had received 11 reports of thrombocytopenia associated with quetiapine, 6 of which were associated with quetiapine alone. In one of these 6 cases, thrombocytopenia recurred 3 months after restarting quetiapine, which had stopped for 1 month.

1. Clark N, *et al.* Quetiapine and leukopenia. *Am J Psychiatry* 2001; **158:** 817–18.
2. Croarkin P, Rayner T. Acute neutropenia in a patient treated with quetiapine. *Psychosomatics* 2001; **42:** 368.
3. Iraqi A. A case report of pancytopenia with quetiapine use. *Am J Geriatr Psychiatry* 2003; **11:** 694.
4. Huynh M, *et al.* Thrombotic thrombocytopenic purpura associated with quetiapine. *Ann Pharmacother* 2005; **39:** 1346–8.
5. Health Canada. Quetiapine: pancreatitis and thrombocytopenia. *Can Adverse React News* 2007; **17** (2): 1–2. Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v17n2_e.pdf (accessed 09/04/08)

Effects on body-weight. The increased risk of weight gain with some atypical antipsychotics is discussed under Adverse Effects of Clozapine, p.981.

Further references.

1. Brecher M, *et al.* Quetiapine and long-term weight change: a comprehensive data review of patients with schizophrenia. *J Clin Psychiatry* 2007; **68:** 597–603.

Effects on carbohydrate metabolism. The increased risk of glucose intolerance and diabetes mellitus with some atypical antipsychotics, including quetiapine, and recommendations for monitoring, are discussed under Adverse Effects of Clozapine, p.981.

Further references for such effects associated with quetiapine use are given below.

1. Koller EA, *et al.* A survey of reports of quetiapine-associated hyperglycemia and diabetes mellitus. *J Clin Psychiatry* 2004; **65:** 857–63.
2. Takahashi M, *et al.* Rapid onset of quetiapine-induced diabetic ketoacidosis in an elderly patient: a case report. *Pharmacopsychiatry* 2005; **38:** 183–4.

Effects on lipid metabolism. The increased risk of hyperlipidaemia with some atypical antipsychotics is discussed under Adverse Effects of Chlorpromazine, p.970. See also Effects on Carbohydrate Metabolism under Adverse Effects of Clozapine, p.981.

Effects on the pancreas. From December 1997 to October 2006, Health Canada[1] had received 9 reports of pancreatitis associated with quetiapine, 5 of which were associated with quetiapine alone. One patient was reported to have developed severe haemorrhagic pancreatitis, and another, necrotising pancreatitis. One report described pancreatitis occurring on two separate occasions in the patient.

1. Health Canada. Quetiapine: pancreatitis and thrombocytopenia. *Can Adverse React News* 2007; **17** (2): 1–2. Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v17n2_e.pdf (accessed 09/04/08)

Effects on the respiratory system. Hyperventilation and respiratory alkalosis have been reported with quetiapine use.[1] Acute respiratory failure developed[2] in a 92-year-old woman with a history of chronic obstructive pulmonary disease who was given a single 50-mg dose of quetiapine.

1. Shelton PS, *et al.* Hyperventilation associated with quetiapine. *Ann Pharmacother* 2000; **34:** 335–7.
2. Jabeen S, *et al.* Acute respiratory failure with a single dose of quetiapine fumarate. *Ann Pharmacother* 2006; **40:** 559–62.

Mania. Although it is used in the treatment of bipolar disorder, quetiapine has been associated with mania. In one report, a 26-year-old man with schizophrenia developed manic symptoms after starting treatment with quetiapine; the symptoms resolved when quetiapine was withdrawn.[1]

1. Lykouras L, *et al.* Manic symptoms associated with quetiapine treatment. *Eur Neuropsychopharmacol* 2003; **13:** 135–6.

Overdosage. Hypotension, tachycardia, and somnolence were the main clinical events seen in a patient who had taken an overdose of 3 g of quetiapine.[1] Tachycardia of an unexpectedly long duration was also noted. Management was symptomatic, including maintenance of fluids. Asymptomatic prolongation of the QT interval was seen in another patient who had taken a 2-g overdose of quetiapine.[2] Her treatment regimen also included risperidone, and the authors warned that considerable QT interval prolongation may occur when patients overdose on quetiapine while taking therapeutic doses of risperidone.

A subsequent report[3] has described a case series of 18 patients who took from 500 mg to 24 g of quetiapine either alone (6 patients) or with other drugs (12). Quetiapine overdosage was primarily associated with CNS and respiratory depression and sinus tachycardia. Four of the 18 patients required mechanical ventilation but no deaths occurred. The corrected QT interval, but not the QT interval, was prolonged, but apart from sinus tachycardia no patient had a dysrhythmia. Seizures occurred in 2 patients and delirium in 3. The patient who took 24 g of quetiapine was found to have had a peak blood concentration of 20.48 micrograms/mL. She had presented 1.5 hours after ingestion and was intubated and treated with gastric lavage followed by activated charcoal. About 2.5 hours later she had a generalised tonic-clonic seizure. The patient was discharged after 40 hours without sequelae. Another analysis[4] considered 14 cases of overdose, the amounts varying from 1.2 to 18 g; there appeared to be no correlation between the amount taken and the serum concentration, nor was severity of intoxication necessarily correlated with greater intake. Toxicity was generally mild, with tachycardia and somnolence as the main presenting symptoms; there were no fatalities.

1. Beelen AP, *et al.* Asymptomatic QTc prolongation associated with quetiapine fumarate overdose in a patient being treated with risperidone. *Hum Exp Toxicol* 2001; **20:** 215–19.
2. Pollak PT, Zbuk K. Quetiapine fumarate overdose: clinical and pharmacokinetic lessons from extreme conditions. *Clin Pharmacol Ther* 2000; **68:** 92–7.
3. Balit CR, *et al.* Quetiapine poisoning: a case series. *Ann Emerg Med* 2003; **42:** 751–8.
4. Hunfeld NG, *et al.* Quetiapine in overdosage: a clinical and pharmacokinetic analysis of 14 cases. *Ther Drug Monit* 2006; **28:** 185–9.

Pregnancy. For comments on the use of some atypical antipsychotics, including quetiapine, during pregnancy, see under Precautions of Clozapine, p.983.

Interactions

The central effects of other CNS depressants, including alcohol, may be enhanced by quetiapine. Quetiapine should be used with caution in patients also receiving antihypertensives or drugs that prolong the QT interval. Quetiapine may antagonise the actions of dopaminergics such as levodopa.

CYP3A4 is the main isoenzyme responsible for cytochrome P450-mediated metabolism of quetiapine and caution is advised when quetiapine is used with potent inhibitors of CYP3A4 such as erythromycin, fluconazole, itraconazole, and ketoconazole; lower doses of quetiapine should be used when given with such drugs. Conversely, enzyme inducers such as carbamazepine and phenytoin may decrease the plasma concentrations of quetiapine, and higher doses of quetiapine may be necessary. Thioridazine has also been reported to increase the clearance of quetiapine.

Antibacterials. In a study involving 19 Chinese patients with schizophrenia taking quetiapine 200 mg twice daily, adding *erythromycin* 500 mg three times daily increased the maximum plasma concentration, area under the concentration-time curve, and terminal elimination half-life of quetiapine by 68, 129, and 92%, respectively. Reductions in plasma concentrations of the metabolites of quetiapine suggested that erythromycin had probably inhibited quetiapine's metabolism by the cytochrome P450 isoenzyme CYP3A4. Modification of dosage was recommended in this patient group taking these two drugs together.[1]

1. Li K-Y, *et al.* Effect of erythromycin on metabolism of quetiapine in Chinese suffering from schizophrenia. *Eur J Clin Pharmacol* 2005; **60:** 791–5.

Antipsychotics. For a report of asymptomatic QT prolongation associated with quetiapine in a patient also receiving *risperidone*, see under Overdosage, above.

Pharmacokinetics

Quetiapine is well absorbed after oral doses and widely distributed throughout the body. Peak plasma concentrations are reached in about 1.5 hours. It is about 83% bound to plasma proteins. Quetiapine is extensively metabolised in the liver by sulfoxidation mediated mainly by the cytochrome P450 isoenzyme CYP3A4 and by oxidation. It is excreted mainly as inactive metabolites with about 73% of a dose appearing in the urine and about 20% in the faeces. The elimination half-life has been reported to be about 6 to 7 hours.

It is distributed into breast milk.

◊ References.

1. DeVane CL, Nemeroff CB. Clinical pharmacokinetics of quetiapine: an atypical antipsychotic. *Clin Pharmacokinet* 2001; **40:** 509–22.
2. Jaskiw GE, *et al.* Pharmacokinetics of quetiapine in elderly patients with selected psychotic disorders. *Clin Pharmacokinet* 2004; **43:** 1025–35. Correction. *ibid.*; 1178.

Uses and Administration

Quetiapine fumarate is a dibenzothiazepine atypical antipsychotic. It is reported to have affinity for serotonin (5-HT_2), histamine (H_1), and adrenergic (α_1 and α_2) receptors as well as dopamine D_1 and D_2 receptors. Quetiapine is used in the treatment of schizophrenia and of bipolar disorder.

Quetiapine is given orally as the fumarate although doses are expressed in terms of the base; 28.8 mg of quetiapine fumarate is equivalent to about 25 mg of quetiapine.

The usual initial daily dose in **schizophrenia** is the equivalent of 50 mg of the base on day one. In the UK, 100 mg is given on day two, 200 mg on day three, and 300 mg on day four; daily doses are given in 2 divided doses. The dosage is then adjusted according to response to a usual range of 300 to 450 mg daily, although 150 mg daily may be adequate for some patients; the maximum recommended dose is 750 mg daily. In the USA, the usual initial daily dose is increased on days two and three in increments of 50 to 150 mg, as tolerated, to a target of 300 to 400 mg daily by day four. The daily dose on the first day is given in 2 divided doses, but may be given in 3 divided doses thereafter. The daily dosage may be further adjusted as necessary in steps of 50 to 100 mg at intervals of not less than 2 days to a usual range similar to that in the UK. A modified-release preparation of quetiapine is also available in some countries for once-daily dosing up to the equivalent of 800 mg daily of the base.

In the treatment of acute manic episodes associated with **bipolar disorder**, the initial dose is 50 mg twice daily on day one, 100 mg twice daily on day two, 150 mg twice daily on day three, and 200 mg twice daily on day four. The dose may then be adjusted according to response to a usual range of 400 to 800 mg daily, although, in some patients, 200 mg daily may be adequate. Increments in dosage should be no greater than 200 mg daily. Quetiapine is also licensed in the USA for use in the depressive phase of bipolar disorder. The initial dose is 50 mg once daily at bedtime increased to 100 mg on day two, 200 mg on day three, and 300 mg on day four. The dose may be further increased to 400 mg on day five and 600 mg on day eight, if necessary. In the USA, quetiapine is also licensed for the maintenance treatment of bipolar disorder as an adjunct to lithium or valproate; patients should be continued on the dose that controlled their initial symptoms.

Quetiapine should be given in reduced doses to the elderly; a recommended starting dose is 25 mg daily, which may be increased every day in increments of 25 to 50 mg according to response; the effective dose range is likely to be lower than in younger adults. Reduced doses are also recommended in patients with hepatic or renal impairment, see below.

Administration in hepatic or renal impairment. Quetiapine should be given in reduced doses to patients with hepatic impairment; a recommended initial oral dose is 25 mg daily, increased in steps of 25 to 50 mg daily according to response. UK licensed product information also recommends a similar dose reduction in patients with renal impairment.

Bipolar disorder. Quetiapine is of benefit for the treatment of mania in patients with bipolar disorder (p.372) and the use of atypical antipsychotics in the management of such patients is increasing. However, there have been individual case reports of quetiapine-induced mania (see above). In some countries, quetiapine is also licensed for use in the depressive phase of bipolar disorder.

References.

1. Sajatovic M, *et al.* Quetiapine alone and added to a mood stabilizer for serious mood disorders. *J Clin Psychiatry* 2001; **62:** 728–32.
2. Vieta E, *et al.* Quetiapine in the treatment of rapid cycling bipolar disorder. *Bipolar Disord* 2002; **4:** 335–40.
3. Delbello MP, *et al.* A double-blind, randomized, placebo-controlled study of quetiapine as adjunctive treatment for adolescent mania. *J Am Acad Child Adolesc Psychiatry* 2002; **41:** 1216–23.
4. Altamura AC, *et al.* Efficacy and tolerability of quetiapine in the treatment of bipolar disorder: preliminary evidence from a 12-month open-label study. *J Affect Disord* 2003; **76:** 267–71.
5. Yatham LN, *et al.* Quetiapine versus placebo in combination with lithium or divalproex for the treatment of bipolar mania. *J Clin Psychopharmacol* 2004; **24:** 599–606. Correction. *ibid.* 2005; **25:** 103.
6. Bowden CL, *et al.* A randomized, double-blind, placebo-controlled efficacy and safety study of quetiapine or lithium as monotherapy for mania in bipolar disorder. *J Clin Psychiatry* 2005; **66:** 111–21.
7. Dando TM, Keating GM. Quetiapine: a review of its use in acute mania and depression associated with bipolar disorder. *Drugs* 2005; **65:** 2533–51.
8. Pini S, *et al.* The role of quetiapine in the treatment of bipolar disorder. *Expert Opin Pharmacother* 2006; **7:** 929–40.
9. Khouzam HR, Singh F. Bipolar disorder: historic perspective, current pharmacologic treatment options and a review of quetiapine. *Expert Rev Neurother* 2006; **6:** 131–44.
10. Keating GM, Robinson DM. Quetiapine: a review of its use in the treatment of bipolar depression. *Drugs* 2007; **67:** 1077–94.
11. Brahm NC, *et al.* Quetiapine for acute mania in bipolar disorder. *Am J Health-Syst Pharm* 2007; **64:** 1045–53.

Parkinsonism. Quetiapine has been tried as an antipsychotic[1-3] in patients with parkinsonism (p.791).

1. Fernandez HH, *et al.* Long-term outcome of quetiapine use for psychosis among Parkinsonian patients. *Mov Disord* 2003; **18:** 510–14.
2. Juncos JL, *et al.* Quetiapine improves psychotic symptoms and cognition in Parkinson's disease. *Mov Disord* 2004; **19:** 29–35.
3. Morgante L, *et al.* Quetiapine and clozapine in parkinsonian patients with dopaminergic psychosis. *Clin Neuropharmacol* 2004; **27:** 153–6. Correction. *ibid.*; 256.

Schizophrenia. A systematic review[1] noted that, although quetiapine is effective for the treatment of schizophrenia, it appeared comparable with classical antipsychotics and risperidone.

The incidence of extrapyramidal effects was lower with quetiapine therapy but the risk of dry mouth and somnolence was higher. Quetiapine was not found to benefit negative symptoms.

1. Srisurapanont M, *et al.* Quetiapine for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 30/05/05).

Tourette's syndrome. When drug treatment is required for tics and behavioural disturbances in Tourette's syndrome (see Tics, p.954) haloperidol or pimozide are commonly used but atypical antipsychotics, including quetiapine, are increasingly being tried.[1-3]

1. Mukaddes NM, Abali O. Quetiapine treatment of children and adolescents with Tourette's disorder. *J Child Adolesc Psychopharmacol* 2003; **13:** 295–9.
2. Little AE, *et al.* Quetiapine in the treatment of tic disorder. *Ann Pharmacother* 2006; **40:** 1472.
3. de Jonge JL, *et al.* Quetiapine in patients with Tourette's disorder: an open-label, flexible-dose study. *J Clin Psychiatry* 2007; **68:** 1148–50.

Preparations

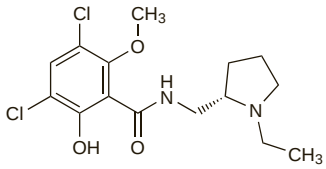
Proprietary Preparations (details are given in Part 3)
Arg.: Quetiazic; Seroquel; Vesparax; ***Austral.:*** Seroquel; ***Austria:*** Seroquel; ***Belg.:*** Seroquel; ***Braz.:*** Seroquel; ***Canad.:*** Seroquel; ***Chile:*** Norsic; Quetidin; Seroquel; ***Cz.:*** Ketilept; Kventiax; Nantarid; Quepita; Questax; Quetin; Seroquel; Stadaquel; ***Denm.:*** Seroquel; ***Fin.:*** Seroquel; ***Ger.:*** Seroquel; ***Gr.:*** Seroquel; ***Hong Kong:*** Seroquel; ***Hung.:*** Ketilept; Seroquel; ***India:*** Quel; Seroquin; Socalm; ***Indon.:*** Seroquel; ***Irl.:*** Seroquel; ***Israel:*** Seroquel; ***Ital.:*** Seroquel; ***Jpn:*** Seroquel; ***Malaysia:*** Seroquel; ***Mex.:*** Seroquel; ***Neth.:*** Seroquel; ***Norw.:*** Seroquel; ***NZ:*** Quetapel; Seroquel; ***Philipp.:*** Seroquel; ***Pol.:*** Ketrel; Seroquel; ***Port.:*** Alzen; Seroquel; ***Rus.:*** Seroquel (Сероквель); ***S.Afr.:*** Seroquel; ***Singapore:*** Seroquel; ***Spain:*** Seroquel; ***Swed.:*** Seroquel; ***Switz.:*** Seroquel; ***Thai.:*** Seroquel; ***Turk.:*** Seroquel; ***UK:*** Seroquel; ***USA:*** Seroquel; ***Venez.:*** Seroquel.

Raclopride *(BAN, rINN)*

A-40664 (raclopride tartrate); FLA-870; Racloprida; Racloprid-ium; Raclopridum; Rakloprid; Rakloprid. (*S*)-3,5-Dichloro-*N*-(1-ethylpyrrolidin-2-ylmethyl)-2-hydroxy-6-methoxybenzamide.

Раклоприд

$C_{15}H_{20}Cl_2N_2O_3$ = 347.2.
CAS — 84225-95-6 (raclopride); 98185-20-7 (raclopride tartrate).



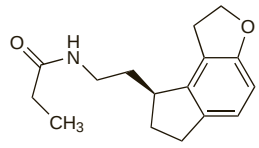
Profile
Raclopride is a substituted benzamide related to sulpiride (p.1028). It has been investigated for the treatment of psychoses. Since it binds selectively and with high affinity to D_2 dopaminergic receptors, raclopride labelled with carbon-11 has been tried as a tracer in computerised tomographic studies of neurological disorders associated with dysfunction of brain D_2 dopaminergic receptors.

Ramelteon *(BAN, USAN, rINN)*

Rameltéon; Ramelteón; Ramelteonum; TAK-375. (-)-*N*-{2-[(8*S*)-1,6,7,8-Tetrahydro-2*H*-indeno[5,4-*b*]furan-8-yl]ethyl}propanamide.

Рамельтеон

$C_{16}H_{21}NO_2$ = 259.3.
CAS — 196597-26-9.
ATC — N05CH02.
ATC Vet — QN05CH02.



Profile
Ramelteon is a melatonin receptor agonist used as a hypnotic in the management of insomnia (p.957), particularly in patients who have difficulty falling asleep. The usual oral dose is 8 mg taken within 30 minutes of bedtime; it should not be taken with or immediately after a high-fat meal. Ramelteon is not recommended for patients with severe hepatic impairment; it should be used with caution in those with moderate impairment.

Ramelteon is metabolised mainly via the cytochrome P450 isoenzyme CYP1A2 and consequently, it should not be used with fluvoxamine, a potent inhibitor of this isoenzyme; it should also be used with caution in patients taking other drugs that inhibit this isoenzyme.

◊ References.

1. Karim A, *et al.* Disposition kinetics and tolerance of escalating single doses of ramelteon, a high-affinity MT and MT melatonin receptor agonist indicated for treatment of insomnia. *J Clin Pharmacol* 2006; **46:** 140–8.
2. Greenblatt DJ, *et al.* Age and gender effects on the pharmacokinetics and pharmacodynamics of ramelteon, a hypnotic agent acting via melatonin receptors MT and MT . *J Clin Pharmacol* 2007; **47:** 485–96.

Preparations

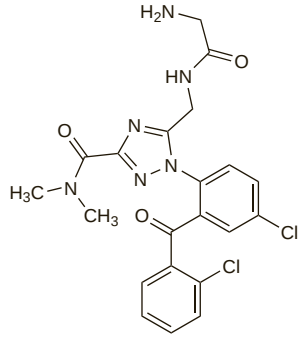
Proprietary Preparations (details are given in Part 3)
Fr.: Rozerem; ***Jpn:*** Rozerem; ***USA:*** Rozerem.

Rilmazafone Hydrochloride *(rINNM)*

Hidrocloruro de rilmazafona; Rilmazafone, Chlorhydrate de; Rilmazafoni Hydrochloridum; 450191-S. 5-[(2-Aminoacetamido)methyl]-1-[4-chloro-2-(*o*-chlorobenzoyl)phenyl]-*N*,*N*-dimethyl-1*H*-1,2,4-triazole-3-carboxamide hydrochloride dihydrate.

Рильмазафона Гидрохлорид

$C_{21}H_{20}Cl_2N_6O_3$,HCl,2H_2O = 547.8.
CAS — 99593-25-6 (rilmazafone); 85815-37-8 (anhydrous rilmazafone hydrochloride).



(rilmazafone)

Profile
Rilmazafone hydrochloride is a hypnotic and sedative used in the short-term treatment of insomnia in usual oral doses of 1 to 2 mg at bedtime; it is also used in similar doses as a premedicant.

Preparations

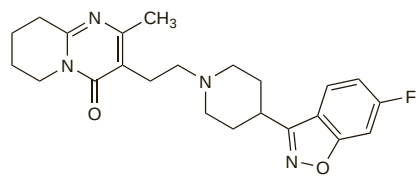
Proprietary Preparations (details are given in Part 3)
Jpn: Rhythmy.

Risperidone *(BAN, USAN, rINN)*

R-64766; Risperidon; Risperidona; Risperidonas; Rispéridone; Risperidoni; Risperidonum; Riszperidon; Rysperydon. 3-{2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl}-6,7,8,9-tetrahydro-2-methylpyrido[1,2-*a*]pyrimidin-4-one.

Рисперидон

$C_{23}H_{27}FN_4O_2$ = 410.5.
CAS — 106266-06-2.
ATC — N05AX08.
ATC Vet — QN05AX08.



Pharmacopoeias. In *Eur.* (see p.vii) and *US.*
Ph. Eur. 6.2 (Risperidone). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane; dissolves in dilute acid solutions. Protect from light.
USP 31 (Risperidone). A white or almost white powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in dichloromethane.

Adverse Effects, Treatment, and Precautions

Although risperidone may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p.969), the incidence and severity of such effects may vary. Risperidone is reported to be less likely to cause sedation or extrapyramidal effects (see also Uses and Administration, below) but agitation may occur more frequently. Other common adverse effects include insomnia, anxiety, and headache. Dyspepsia, nausea and vomiting, abdominal pain, constipation, blurred vision, sexual dysfunction including priapism, urinary incontinence, rash and other allergic reactions, drowsiness, concentration difficulties, dizziness, fatigue, and rhinitis have been reported less commonly. In addition to orthostatic hypotension, hypertension has been reported infrequently. Other adverse effects with risperidone include cerebrovascular accidents, tachycardia, weight gain, oedema, increased liver enzyme values, and decreases in neutrophil or thrombocyte counts. Risperidone may cause dose-dependent increases in prolactin levels. In rare cases, hyperglycaemia and exacerbation of pre-existing diabetes mellitus have also been reported. Clinical monitoring for hyperglycaemia has been recommended, especially in patients with or at risk of developing diabetes. Other rare effects include seizures, body temperature dysregulation, hyponatraemia, neuroleptic malignant syndrome, and tardive dyskinesia.

Risperidone should be used with caution in patients with cardiovascular disease, including conditions associated with QT prolongation, or conditions predisposing to hypotension. Caution is also recommended in patients with a history of or at risk of developing cerebrovascular disease, in patients with Parkinson's disease or epilepsy, and in patients with hepatic or renal impairment.

Risperidone may affect the performance of skilled tasks such as driving.

Gradual withdrawal of risperidone is recommended because of the risk of withdrawal symptoms, including sweating, nausea and vomiting, and rebound psychosis, with abrupt cessation.

Breast feeding. From the study of concentrations of risperidone and its active metabolite, 9-hydroxyrisperidone, in the breast milk of a mother receiving 6 mg daily by mouth, it was estimated that a breast-fed infant would ingest the daily equivalent of 4.3% (as risperidone equivalents) of the weight-adjusted maternal dose.[1] Later case reports[2] of 3 women receiving risperidone 3 mg daily, 4 mg daily, and 1.5 mg daily, by mouth, estimated that a breast-fed infant would receive the daily equivalent of 2.3%, 2.8%, and 4.7%, respectively, of the weight-adjusted maternal dose. Where breast feeding occurred, in the latter 2 cases, no adverse effects were reported in the breast-fed infants; risperidone and 9-hydroxyrisperidone were not detected in the plasma of either infant.

Licensed product information states that patients receiving risperidone should not breast feed; the US information also recommends that patients should not breast feed for at least 12 weeks after intramuscular injection.

1. Hill RC, *et al.* Risperidone distribution and excretion into human milk: case report and estimated infant exposure during breast-feeding. *J Clin Psychopharmacol* 2000; **20:** 285–6.
2. Ilett KF, *et al.* Transfer of risperidone and 9-hydroxyrisperidone into human milk. *Ann Pharmacother* 2004; **38:** 273–6.

Dementia. After analysis of data from controlled studies there was evidence that the use of risperidone in elderly patients with dementia appeared to be associated with an increased risk of cerebrovascular adverse effects such as stroke and transient ischaemic attacks. In 4 studies, involving 764 such patients treated with risperidone, there were 29 cases of cerebrovascular adverse events (4 fatal) versus 7 cases (1 fatal) in 466 patients given placebo. Postmarketing data for elderly dementia patients, representing over 2.4 million patient-years of exposure, included 37 cases, of which 16 were fatal.[1]

The UK CSM[2] have therefore recommended that risperidone should not be used to treat behavioural problems in elderly patients with dementia. Similarly, the CSM[2] and the EMEA[3] have recommended that olanzapine should not be used to treat behavioural problems or dementia-related psychosis in elderly patients with dementia after analysis of placebo-controlled studies revealed a threefold increase in cerebrovascular adverse effects including stroke and a twofold increase in all-cause mortality. It was considered[2] that the risk may not be confined to use in dementia and should be considered relevant to any patient with a