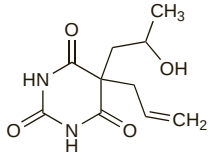
Proxibarbal *(rINN)*

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.

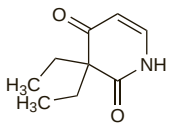
Preparations
Proprietary Preparations (details are given in Part 3)
Hung.: Vasalgin.

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.



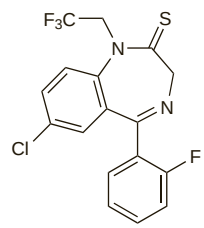
Profile
Pyrithyldione has been given in preparations with diphenhydramine in the short-term management of insomnia but there have been reports of agranulocytosis associated with the use of this combination.

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.

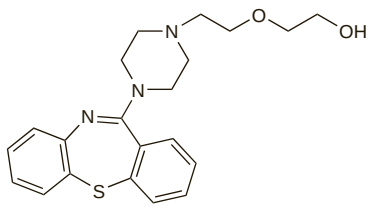
Quetiapine Fumarate

(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)