Preparations

BP 2008: Clomethiazole Capsules; Clomethiazole Intravenous Infusion; Clomethiazole Oral Solution.

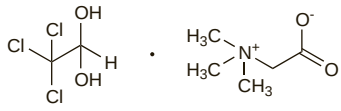
Proprietary Preparations (details are given in Part 3)
Austral.: Heminevrin; ***Belg.:*** Distraneurine†; ***Cz.:*** Heminevrin; ***Denm.:*** Heminevrin; ***Fin.:*** Heminevrin†; ***Ger.:*** Distraneurin; ***Gr.:*** Distraneurine; Heminevrin; ***Hong Kong:*** Heminevrin†; ***Hung.:*** Heminevrin; ***Irl.:*** Heminevrin; ***Norw.:*** Heminevrin; ***Pol.:*** Heminevrin; ***Spain:*** Distraneurine; ***Swed.:*** Heminevrin; ***Switz.:*** Distraneurin; ***UK:*** Heminevrin.

Cloral Betaine *(BAN, rINN)*

Chloral Betaine *(USAN)*; Cloral betaína; Cloral Bétaïne; Cloralum Betainum; Compound 5107. An adduct of cloral hydrate and betaine.

Хлораль Бетаин

$C_7H_{12}Cl_3NO_3,H_2O$ = 282.5.
CAS — 2218-68-0.



Profile

Cloral betaine rapidly dissociates in the stomach to release cloral hydrate and has actions and uses similar to those of cloral hydrate (below). It is given orally in the short-term management of insomnia (p.957), as tablets containing 707 mg (equivalent to about 414 mg of cloral hydrate). The usual hypnotic dose is one or two tablets taken at night with water or milk. The maximum daily dose is five tablets (equivalent to about 2 g of cloral hydrate). A reduction in dosage may be appropriate in frail elderly patients or in those with hepatic impairment.

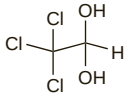
Preparations

Proprietary Preparations (details are given in Part 3)
UK: Somnwell; Welldorm.

Cloral Hydrate

Chloral Hydrate *(BAN)*; Chloral, hydrate de; Chloralhydrát; Chlorali hydras; Chloralio hidratas; Chloralu wodzian; Cloral, hidrato de; Kloraalihydraatti; Kloral Hidrat; Klorál-hidrát; Kloralhydrat. 2,2,2-Trichloroethane-1,1-diol.

$C_2H_3Cl_3O_2$ = 165.4.
CAS — 302-17-0.
ATC — N05CC01.
ATC Vet — QN05CC01.



NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of cloral hydrate:
Jellies; Jelly beans; Joy Juice; Knockout Drops; Knock out drops; Mickey; Mickeys; Mickey Finn; Mickey Finns; Peter; Torpedo.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Cloral Hydrate). Colourless, transparent crystals. Very soluble in water; freely soluble in alcohol. A 10% solution in water has a pH of 3.5 to 5.5. Store in airtight containers.

USP 31 (Cloral Hydrate). Colourless, transparent, or white crystals having an aromatic, penetrating, and slightly acrid odour. It volatilises slowly on exposure to air and melts at about 55°. Soluble 1 in 0.25 of water, 1 in 1.3 of alcohol, 1 in 2 of chloroform, and 1 in 1.5 of ether; very soluble in olive oil. Store in airtight containers.

Incompatibility. Cloral hydrate is reported to be incompatible with alkalis, alkaline earths, alkali carbonates, soluble barbiturates, borax, tannin, iodides, oxidising agents, permanganates, and alcohol (cloral alcoholate may crystallise out). It forms a liquid mixture when triturated with many organic compounds, such as camphor, menthol, phenazone, phenol, thymol, and quinine salts.

Dependence and Withdrawal, Adverse Effects, and Treatment

Cloral hydrate has an unpleasant taste and is corrosive to skin and mucous membranes unless well diluted. The most frequent adverse effect is gastric irritation; abdominal distension and flatulence may also occur. CNS effects such as drowsiness, lightheadedness, ataxia, headache, and paradoxical excitement, hallucinations, nightmares, delirium, and confusion (sometimes with paranoia) occur occasionally. Hypersensitivity reactions include skin rashes (erythema multiforme and Stevens-Johnson syndrome have been reported with the related compound triclofos). Ketonuria may occur.

The effects of acute overdosage resemble acute barbiturate intoxication (see Amobarbital, p.962 and below), and are managed similarly. In addition the irritant effect may cause initial vomiting, and gastric necrosis leading to strictures. Cardiac arrhythmias have been reported. Jaundice may follow liver damage, and albuminuria may follow kidney damage.

Tolerance may develop and dependence may occur. Features of dependence and withdrawal are similar to those of barbiturates (see Amobarbital, p.962).

Incidence of adverse effects. In a drug surveillance programme,[1] adverse effects of cloral hydrate, which were reversible, occurred in 2.3% of 1130 patients evaluated and included gastrointestinal symptoms (10 patients), CNS depression (20), and skin rash (5). In 1 patient the prothrombin time was increased; in 1 patient hepatic encephalopathy seemed to worsen; and bradycardia developed in 1 patient. In another such programme, adverse effects occurred in about 2% of 5435 patients given cloral hydrate.[2] Three reactions were described as life-threatening.

1. Shapiro S, *et al*. Clinical effects of hypnotics II: an epidemiologic study. *JAMA* 1969; **209:** 2016–20.
2. Miller RR, Greenblatt DJ. Clinical effects of chloral hydrate in hospitalized medical patients. *J Clin Pharmacol* 1979; **19:** 669–74.

Carcinogenicity. Cloral hydrate has been widely used as a sedative, especially in children. Concern over warnings that cloral hydrate was carcinogenic in *rodents*[1] has prompted some experts, including the American Academy of Pediatrics, to review the relative risks of the medical use of this drug.[2,3] The original warnings appear to have been based, in part, on the assumption that cloral hydrate was a reactive metabolite of trichloroethylene and was responsible for its carcinogenicity, but there is evidence to suggest that the carcinogenicity of trichloroethylene is due to a reactive intermediate epoxide metabolite. Studies *in vitro* indicate that cloral hydrate can damage chromosomes in some mammalian test systems but there have been no studies of the carcinogenicity of cloral hydrate in humans. Some long-term studies in *mice* have linked cloral hydrate with the development of hepatic adenomas or carcinomas. However, it was noted that cloral hydrate was not the only sedative that had been shown to be a carcinogen in experimental *animals*. The American Academy of Pediatrics considered cloral hydrate to be an effective sedative with a low incidence of acute toxicity when given short-term as recommended and, although the information on carcinogenicity was of concern, it was not sufficient to justify the risk associated with the use of less familiar sedatives. There was no evidence in infants or children showing that any of the available alternatives were safer or more effective. However, the use of repetitive dosing with cloral hydrate to maintain prolonged sedation in neonates and other children was of concern because of the potential for accumulation of drug metabolites and resultant toxicity. A recent cohort study[4] found no persuasive evidence to support a relationship between the use of cloral hydrate and the development of cancer. However, the statistical power was low for weak associations, particularly for some individual cancer sites.

1. Smith MT. Chloral hydrate warning. *Science* 1990; **250:** 359.
2. Steinberg AD. Should chloral hydrate be banned? *Pediatrics* 1993; **92:** 442–6.
3. American Academy of Pediatrics Committee on Drugs and Committee on Environmental Health. Use of chloral hydrate for sedation in children. *Pediatrics* 1993; **92:** 471–3.
4. Haselkorn T, *et al*. Short-term chloral hydrate administration and cancer in humans. *Drug Safety* 2006; **29:** 67–77.

Effects on the CNS. A 2-year-old child[1] had the first of 2 seizures 60 minutes after receiving cloral hydrate 70 mg/kg for sedation.

1. Muñoz M, *et al*. Seizures caused by chloral hydrate sedative doses. *J Pediatr* 1997; **131:** 787–8.

Hyperbilirubinaemia. Small retrospective studies[1] have suggested that prolonged use of cloral hydrate in neonates may be associated with the development of hyperbilirubinaemia. This may possibly be related to the prolonged half-life of the metabolite trichloroethanol in neonates.

1. Lambert GH, *et al*. Direct hyperbilirubinemia associated with chloral hydrate administration in the newborn. *Pediatrics* 1990; **86:** 277–81.

Overdosage. The general management of poisoning with cloral hydrate resembles that for barbiturates (see Treatment of Adverse Effects, under Amobarbital, p.962). Activated charcoal may be given orally to adults and children within 1 hour of ingestion of more than 30 mg/kg, provided that the airway can be protected; the value of gastric decontamination for overdose is uncertain. Of 76 cases of cloral hydrate poisoning reported to the UK National Poisons Information Service (NPIS), 47 were severe.[1] Of 39 adults, 12 had cardiac arrhythmias including 5 with cardiac arrest. Antiarrhythmic drugs were recommended unless obviously contra-indicated. Haemoperfusion through charcoal or haemodialysis was recommended for patients in prolonged coma. Cardiac arrhythmias and CNS depression were also major features of 12 cases of cloral hydrate overdosage reported from Australia.[2] Lidocaine was not always successful in controlling arrhythmias, but propranolol was successful in all 7 patients in whom it was used. It was noted that resistant arrhythmias, particularly ventricular fibrillation, ventricular tachycardia, and supraventricular tachycardia, were the usual cause of death in patients who had taken an overdosage of cloral hydrate. Although there had been no controlled studies of antiarrhythmic therapy in overdosage with cloral hydrate, the successful use of beta blockers appeared to be a recurring feature in reports in the literature. Indeed, the UK NPIS notes that tachyarrhythmias usually respond readily to an intravenous beta blocker such as esmolol or propranolol.

Giving flumazenil produced an increased level of consciousness, pupillary dilatation, and return of respiratory rate and blood pressure towards normal in a patient who had taken an overdosage of cloral hydrate.[3]

1. Wiseman HM, Hampel G. Cardiac arrhythmias due to chloral hydrate poisoning. *BMJ* 1978; **2:** 960.
2. Graham SR, *et al*. Overdose with chloral hydrate: a pharmacological and therapeutic review. *Med J Aust* 1988; **149:** 686–8.
3. Donovan KL, Fisher DJ. Reversal of chloral hydrate overdose with flumazenil. *BMJ* 1989; **298:** 1253.

Precautions

Cloral hydrate should not be used in patients with marked hepatic or renal impairment or severe cardiac disease, and oral dosage is best avoided in the presence of gastritis. As with all sedatives, it should be used with caution in those with respiratory insufficiency.

Cloral hydrate can cause drowsiness that may persist the next day; affected patients should not drive or operate machinery. Prolonged use and abrupt withdrawal of cloral hydrate should be avoided to prevent precipitation of withdrawal symptoms. Repeated doses in infants and children may lead to accumulation of metabolites and thereby increase the risk of adverse effects. Use is best avoided during pregnancy.

Cloral hydrate may interfere with some tests for urinary glucose or 17-hydroxycorticosteroids.

Breast feeding. The American Academy of Pediatrics[1] states that, although usually compatible with breast feeding, use of cloral hydrate by breast-feeding mothers has been reported to cause sleepiness in the infant.

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)

Neonates. The half-life of trichloroethanol, an active metabolite of cloral hydrate, is prolonged in neonates;[1] values of up to 66 hours have been reported in some studies. Short-term sedation in the neonate with single oral doses of 25 to 50 mg/kg of cloral hydrate is considered[1] to be probably relatively safe, but repeated dosage carries the risk of accumulation of metabolites which may result in serious toxicity. Toxic reactions may occur even after the drug has been stopped since the metabolites may accumulate for several days.

1. Jacqz-Aigrain E, Burtin P. Clinical pharmacokinetics of sedatives in neonates. *Clin Pharmacokinet* 1996; **31:** 423–43.

Obstructive sleep apnoea. Children with obstructive sleep apnoea could be at risk from life-threatening respiratory obstruction if cloral hydrate is used for sedation. Details of 2 such children who suffered respiratory failure after sedation with cloral hydrate for lung function studies have been reported.[1]

1. Biban P, *et al*. Adverse effect of chloral hydrate in two young children with obstructive sleep apnea. *Pediatrics* 1993; **92:** 461–3.

Porphyria. UK licensed product information recommends that cloral hydrate should not be used in patients with porphyria, although some[1] consider it safe; caution would seem appropriate.

1. Welsh Medicines Information Centre. Drugs that are considered to be safe for use in acute porphyrias. Available at: http://www.wmic.wales.nhs.uk/pdfs/porphyria/PorphyriaSafeList.pdf (accessed 24/06/08)

Interactions

The sedative effects of cloral hydrate are enhanced by other CNS depressants such as alcohol (the 'Mickey Finn' of detective fiction), barbiturates, and other sedatives.

Cloral hydrate may alter the effects of coumarin anticoagulants (see Warfarin, p.1430). A hypermetabolic state, apparently due to displacement of thyroid hormones from their binding proteins, has been reported in patients given an intravenous dose of furosemide subsequent to cloral hydrate.

Pharmacokinetics

Cloral hydrate is rapidly absorbed from the gastrointestinal tract and starts to act within 30 minutes of oral doses. It is widely distributed throughout the body. It is rapidly metabolised to trichloroethanol and trichloroacetic acid (p.1620) in the erythrocytes, liver, and other tissues. It is excreted partly in the urine as trichloroethanol and its glucuronide (urochloralic acid) and as trichloroacetic acid. Some is also excreted in the bile.

Trichloroethanol is the active metabolite, and passes into the CSF, into breast milk, and across the placenta. The half-life of trichloroethanol in plasma is reported to range from about 7 to 11 hours but is considerably prolonged in the neonate. Trichloroacetic acid has a plasma half-life of several days.

Uses and Administration

Cloral hydrate is a hypnotic and sedative with properties similar to those of the barbiturates. It is used in the short-term management of insomnia (p.957) and has been used for sedation and as a sedative for premedication (p.1780); its use as a hypnotic, particularly in children, is now limited. It has been widely used for

sedation of children before diagnostic, dental, or medical procedures (but see under Carcinogenicity above).

Externally, cloral hydrate has a rubefacient action and has been used as a counter-irritant.

Cloral hydrate is given by mouth as an oral liquid or as gelatin capsules with cloral hydrate dissolved in a suitable vehicle. It has also been dissolved in a bland fixed oil and given by enema or as suppositories.

It should not be given as tablets because of the risk of damage to the mucous membrane of the alimentary tract.

The usual oral hypnotic dose in adults is 0.5 to 2 g given as a single dose at night; as a sedative 250 mg can be given three times daily to a maximum daily dose of 2 g. Oral dosage forms should be taken well diluted or with plenty of water or milk. The *BNFC* suggests that children aged 1 month to 12 years be given 30 to 50 mg/kg to a maximum single dose of 1 g by mouth as a hypnotic (but see above); those aged 12 to 18 years may be given 0.5 to 1 g. Although not licensed in the UK for sedation of children before a painless procedure, the *BNFC* suggests the following oral doses, given 45 to 60 minutes beforehand: 1 month to 12 years, 30 to 50 mg/kg (maximum of 1 g), although up to 100 mg/kg (maximum of 2 g) may be used with respiratory monitoring; 12 to 18 years, 1 to 2 g. The *BNFC* states that the doses above may be given rectally if the oral route is unavailable. In the USA, a suggested oral or rectal sedative dose for children is 8.3 mg/kg three times daily to a maximum daily dose of 1.5 g; a dose of 20 to 25 mg/kg has been given as a premedicant prior to EEG evaluation.

A reduction in dosage may be appropriate in frail elderly patients or in those with hepatic impairment.

Derivatives of cloral hydrate, such as cloral betaine (above), chloralose (p.2037), and dichloralphenazone (p.994), which break down in the body to yield cloral hydrate, have been used similarly.

◊ References.

1. McCarver-May DG, *et al.* Comparison of chloral hydrate and midazolam for sedation of neonates for neuroimaging studies. *J Pediatr* 1996; **128:** 573–6.
2. Napoli KL, *et al.* Safety and efficacy of chloral hydrate sedation in children undergoing echocardiography. *J Pediatr* 1996; **129:** 287–91.

Preparations

USP 31: Chloral Hydrate Capsules; Chloral Hydrate Syrup.

Proprietary Preparations (details are given in Part 3)
Ger.: Chloraldurat; ***Switz.:*** Chloraldurat; Medianox; Nervifene; ***UK:*** Welldorm; ***USA:*** Aquachloral; Somnote.

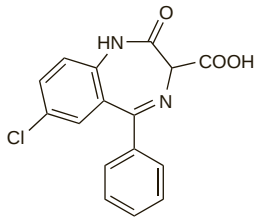
Multi-ingredient: ***Belg.:*** Dentophar; Sedemol; Sulfa-Sedemol; Synthol; ***Fr.:*** Bain de Bouche Lipha; ***Rus.:*** Efcamon (Эфкамон); ***Spain:*** Dentol Topico; ***Turk.:*** Dilan.

Clorazepic Acid *(BAN)*

Clorazépico, ácido. 7-Chloro-2,3-dihydro-2,2-dihydroxy-5-phenyl-1*H*-1,4-benzodiazepine-3-carboxylic acid.

$C_{16}H_{11}ClN_2O_3$ = 314.7.

CAS — 23887-31-2; 20432-69-3.



Clorazepate Monopotassium *(USAN)*

Abbott-39083; 4311-CB; Clorazepato monopotásico. Potassium 7-chloro-2,3-dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepine-3-carboxylate.

$C_{16}H_{10}ClKN_2O_3$ = 352.8.

CAS — 5991-71-9.

Dipotassium Clorazepate *(BANM, rINN)*

Abbott-35616; AH-3232; 4306-CB; Clorazépate dipotassique; Clorazepate Dipotassium *(USAN)*; Clorazepato de dipotasio; Dikalii clorazepas; Dikalio klorazepatas; Dikaliumkloratsepaatti; Dikaliumklorazepat; Dikálium-klórazepát; Kalii Clorazepas; Kaliumkloratsepaatti; Klaiumklorazepat; Klorazepát didraselná sůl; Klorazepat Dipotasyum; Potassium Clorazepate. Compound of Potassium 7-chloro-2,3-dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepine-3-carboxylate with potassium hydroxide.

Дикалия Клоразепат

$C_{16}H_{11}ClK_2N_2O_4$ = 408.9.

CAS — 57109-90-7.

ATC — N05BA05.

ATC Vet — QN05BA05.

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

Ph. Eur. 6.2 (Dipotassium Clorazepate). A white or light yellow, crystalline powder. Solutions in water and in alcohol are unstable and should be used immediately. Freely soluble or very soluble in water; very slightly soluble in alcohol; practically insoluble in dichloromethane. Store in airtight containers. Protect from light.

USP 31 (Clorazepate Dipotassium). A light yellow, crystalline powder which darkens on exposure to light. Soluble in water but, upon standing, may precipitate from the solution; slightly soluble in alcohol and in isopropyl alcohol; practically insoluble in acetone, in chloroform, in dichloromethane, in ether, and in benzene. Store under nitrogen in airtight containers. Protect from light.

Dependence and Withdrawal

As for Diazepam, p.987.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p.987.

Effects on the liver. Jaundice and hepatic necrosis has been associated with clorazepate.[1]

1. Parker JLW. Potassium clorazepate (Tranxene)-induced jaundice. *Postgrad Med J* 1979; **55:** 908–910.

Effects on the nervous system. For reference to extrapyramidal disorders associated with the use of benzodiazepines, including clorazepate, see Diazepam, p.988.

Porphyria. Clorazepate has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

As for Diazepam, p.989.

Pharmacokinetics

Clorazepate is decarboxylated rapidly at the low pH in the stomach to form desmethyldiazepam (nordazepam, see p.1012), which is quickly absorbed.

◊ References.

1. Ochs HR, *et al.* Comparative single-dose kinetics of oxazolam, prazepam, and clorazepate: three precursors of desmethyldiazepam. *J Clin Pharmacol* 1984; **24:** 446–51.
2. Bertler Å, *et al.* Intramuscular bioavailability of chlorazepate as compared to diazepam. *Eur J Clin Pharmacol* 1985; **28:** 229–30.

Uses and Administration

Clorazepate is a long-acting benzodiazepine with general properties similar to those of diazepam (p.992). It is mainly used in the short-term treatment of anxiety disorders (p.952), as an adjunct in the management of epilepsy, and in the alcohol withdrawal syndrome (p.1626).

Dipotassium clorazepate is usually given orally but preparations for intravenous or intramuscular use are also available in some countries. Modified-release preparations given once daily are available in some countries for maintenance therapy.

In the UK, an oral dose of 7.5 mg of dipotassium clorazepate was given up to three times daily for the treatment of anxiety. In the USA rather higher doses have been recommended; 15 to 60 mg of dipotassium clorazepate may be given daily, in divided doses or as a single dose at night.

Up to 90 mg has been given daily in divided doses in the management of **epilepsy** or the **alcohol withdrawal syndrome**. Children aged between 9 and 12 years may be given a maximum of 60 mg daily in the management of epilepsy.

Reduced doses should be given to elderly or debilitated patients.

Preparations

USP 31: Clorazepate Dipotassium Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Justum; Tencilan; Tranxilium; ***Austria:*** Tranxilium; ***Belg.:*** Tranxene; Uni-Tranxene; ***Braz.:*** Tranxilene; ***Canad.:*** Novo-Clopate; Tranxene†; ***Chile:*** Calner; Modival†; Tranxilium; ***Cz.:*** Tranxene†; ***Fr.:*** Tranxene; ***Ger.:*** Tranxilium; ***Gr.:*** Tranxene; ***Hong Kong:*** Tranxene; ***Irl.:*** Tranxene†; ***Israel:*** Tranxal; ***Ital.:*** Transene; ***Malaysia:*** Sanor†; ***Mex.:*** Tranxene; ***Neth.:*** Tranxene; Tranxilium; ***Philipp.:*** Tranxene; ***Pol.:*** Cloranxen; Tranxene; ***Port.:*** Medipax; Tranxene; ***S.Afr.:*** Tranxene; ***Singapore:*** Tranxene; ***Spain:*** Tranxilium; ***Switz.:*** Tranxilium; ***Thai.:*** Anxielax; Cloramed; Cloraxene; Diposef†; Dipot; Flulium; Manotran; Polizep; Pomadom; Posene; Sanor†; Serene; Trancap; Tranclor; Trancon; Tranxene; Zetran; ***Turk.:*** Anksen; Tranxilene; ***UK:*** Tranxene†; ***USA:*** Gen-Xene†; Tranxene; ***Venez.:*** Tranxen.

Multi-ingredient: ***Arg.:*** Euciton Complex; Maxitratobes; Tranxilium Digest; Vegestabil; ***Fr.:*** Noctran; ***Spain:*** Dorken.

Clotiapine *(BAN, rINN)*

Clothiapine *(USAN)*; Clotiapina; Clotiapinum; HF-2159. 2-Chloro-11-(4-methylpiperazin-1-yl)dibenzo[*b,f*][1,4]thiazepine.

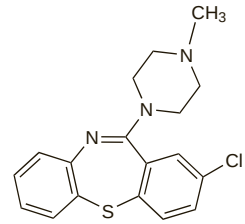
Клотиапин

$C_{18}H_{18}ClN_3S$ = 343.9.

CAS — 2058-52-8.

ATC — N05AX09.

ATC Vet — QN05AX09.



Profile

Clotiapine is a dibenzothiazepine antipsychotic with general properties similar to those of the phenothiazines (see Chlorpromazine, p.969). It is used in a variety of psychiatric disorders including schizophrenia (p.955), mania (see Bipolar Disorder, p.372), and anxiety (p.952). It is given orally in doses ranging from 10 to 200 mg daily in divided doses; up to 360 mg daily has been given in severe or resistant psychoses. It may also be given by slow intravenous or deep intramuscular injection.

Psychoses. A systematic review[1] found that good evidence to support the use of clotiapine over other treatments in acute psychotic illness was lacking.

1. Berk M, *et al.* Clotiapine for acute psychotic illnesses. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 21/08/08).

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Etumina; ***Belg.:*** Etumine; ***Israel:*** Entumin; ***Ital.:*** Entumin; ***S.Afr.:*** Etomine; ***Spain:*** Etumina; ***Switz.:*** Entumine.

Clotiazepam *(rINN)*

Clotiazépam; Clotiazepamum; Y-6047. 5-(2-Chlorophenyl)-7-ethyl-1,3-dihydro-1-methyl-2*H*-thieno[2,3-e]-1,4-diazepin-2-one.

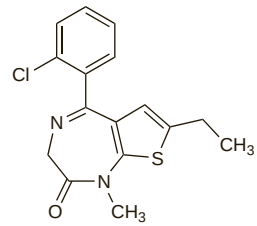
Клотиазепам

$C_{16}H_{15}ClN_2OS$ = 318.8.

CAS — 33671-46-4.

ATC — N05BA21.

ATC Vet — QN05BA21.



Pharmacopoeias. In *Jpn.*

Profile

Clotiazepam is a short-acting thienodiazepine with general properties similar to those of diazepam (p.986). A usual oral daily dose for the short-term management of anxiety disorders (p.952) is 5 to 15 mg given in divided doses but up to 60 mg daily has been used. For sleep disorders (p.957) 10 mg has been given as a single dose at night. An oral dose of 10 to 15 mg has been given for premedication (see Anaesthesia, p.1780). Reduced doses may be required in elderly or debilitated patients.

◊ References.

1. Jibiki I, *et al.* Beneficial effect of high-dose clotiazepam on intractable auditory hallucinations in chronic schizophrenic patients. *Eur J Clin Pharmacol* 1994; **46:** 367–9.

Effects on the liver. Development of hepatitis in a 65-year-old woman was attributed to clotiazepam begun 7 months earlier.[1] The patient took triazolam and lorazepam without any apparent effect on the liver, and it was speculated that the hepatotoxic effect of clotiazepam was related to the thiophene ring present in the chemical structure.

1. Habersetzer F, *et al.* Clotiazepam-induced acute hepatitis. *J Hepatol* 1989; **9:** 256–9.

Porphyria. Clotiazepam is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Clozan; ***Chile:*** Rize; ***Fr.:*** Veratran; ***Ital.:*** Rizen; Tienor; ***Jpn:*** Rize; ***Spain:*** Distensan.