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.

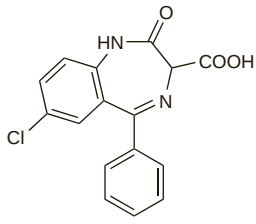
Multi-ingredient: ***Belg.:*** Dentophar; Sedemol; Sulfa-Sedemol; Synthol; ***Fr.:*** Bain de Bouche Lipha; ***Rus.:*** Efcamon (Эфкамон); ***Spain:*** Dentol Topico; ***Turk.:*** Dilan.

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.

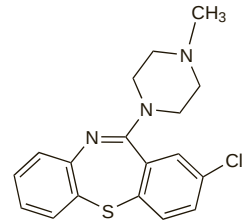
Клотиапин

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

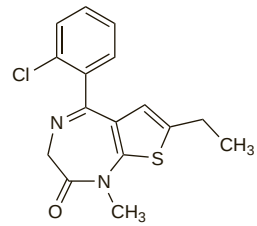
Клотиазепам

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