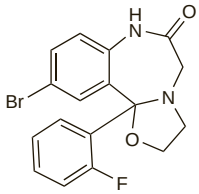
Haloxazolam *(rINN)*

Haloxazolamum. 10-Bromo-11b-(2-fluorophenyl)-2,3,7,11b-tetrahydrooxazolo[3,2-*d*][1,4]benzodiazepin-6(5*H*)-one.

Галоксазолам

$C_{17}H_{14}BrFN_2O_2$ = 377.2.

CAS — 59128-97-1.



Pharmacopoeias. In *Jpn.*

Profile

Haloxazolam is a benzodiazepine with general properties similar to those of diazepam (p.986). It has been given orally as a hypnotic in the short-term management of insomnia.

Hexobarbital *(BAN, rINN)*

Enhexymalum; Enimal; Heksobarbitaali; Heksobarbitalis; Hexobarbitál; Hexobarbitalum; Hexobarbitone; Methexenyl; Methylcyclohexenylmethyl-barbitursäure; Methylhexabarbital. 5-(Cyclohex-1-enyl)-1,5-dimethylbarbituric acid.

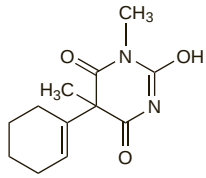
Гексобарбитал

$C_{12}H_{16}N_2O_3$ = 236.3.

CAS — 56-29-1.

ATC — N01AF02; N05CA16.

ATC Vet — QN01AF02; QN05CA16.



NOTE. The name ciclobarbital (see Cyclobarbital, p.986) has sometimes been applied to hexobarbital.

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

Ph. Eur. 6.2 (Hexobarbital). A white or almost white, crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol. Forms water-soluble compounds with alkali hydroxides and carbonates and with ammonia.

Hexobarbital Sodium *(BANM, rINNM)*

Enhexymalnatrium; Hexenalum; Hexobarbital sódico; Hexobarbital Sodique; Hexobarbitalum Natricum; Hexobarbitone Sodium; Natrii Hexobarbitalum; Sodium Hexobarbital; Soluble Hexobarbitone. Sodium 5-(cyclohex-1-enyl)-1,5-dimethylbarbiturate.

Натрий Гексобарбитал

$C_{12}H_{15}N_2NaO_3$ = 258.2.

CAS — 50-09-9.

ATC — N01AF02; N05CA16.

ATC Vet — QN01AF02; QN05CA16.

Profile

Hexobarbital is a barbiturate with the general properties of amobarbital (p.961). It has been used as a hypnotic and sedative but barbiturates are no longer considered appropriate for such purposes.

Preparations

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

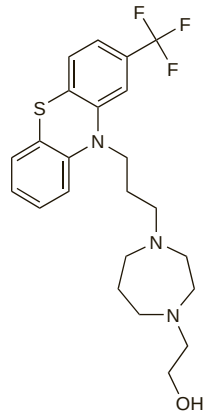
Homofenazine Hydrochloride *(rINNM)*

D-775 (homofenazine); HFZ (homofenazine); Hidrocloruro de homofenazina; Homoféназine, Chlorhydrate d'; Homofenazini Hydrochloridum. 2-{Hexahydro-4-[3-(2-trifluoromethylphenothiazin-10-yl)propyl]-1,4-diazepin-1-yl}ethanol dihydrochloride.

Гомофеназина Гидрохлорид

$C_{23}H_{28}F_3N_3OS,2HCl$ = 524.5.

CAS — 3833-99-6 (homofenazine); 1256-01-5 (homofenazine hydrochloride).



(homofenazine)

Profile

Homofenazine hydrochloride is a phenothiazine with general properties similar to those of chlorpromazine (p.969). It has been used in the management of neuropsychiatric disorders.

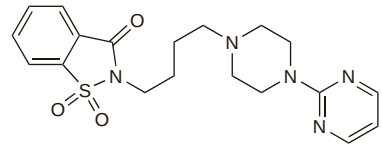
Ipsapirone Hydrochloride *(BANM, USAN, rINNM)*

Bay-q-7821; Hidrocloruro de ipsapirona; Ipsapirone, Chlorhydrate d'; Ipsapironi Hydrochloridum; TVX-Q-7821. 2-[4-(4-Pyrimidin-2-ylpiperazin-1-yl)butyl]-1,2-benzothiazol-3(2*H*)-one 1,1-dioxide hydrochloride.

Ипсапирона Гидрохлорид

$C_{19}H_{23}N_5O_3S,HCl$ = 437.9.

CAS — 95847-70-4 (ipsapirone); 92589-98-5 (ipsapirone hydrochloride).



(ipsapirone)

Profile

Ipsapirone is structurally related to buspirone (p.965). It has been investigated as the hydrochloride for the treatment of anxiety disorders and depression.

Action. Ipsapirone is a partial agonist at serotonin (hydroxytryptamine, 5-HT) receptors of the 5-HT_{1A} subtype. For reference to the actions and potential uses of such drugs, see Buspirone, p.966.

References.

1. Cutler NR, *et al.* A double-blind, placebo-controlled study comparing the efficacy and safety of ipsapirone versus lorazepam in patients with generalized anxiety disorder: a prospective multicenter trial. *J Clin Psychopharmacol* 1993; **13:** 429–37.
2. Fuhr U, *et al.* Absorption of ipsapirone along the human gastrointestinal tract. *Br J Clin Pharmacol* 1994; **38:** 83–6.
3. Mandos LA, *et al.* Placebo-controlled comparison of the clinical effects of rapid discontinuation of ipsapirone and lorazepam after 8 weeks of treatment for generalized anxiety disorder. *Int Clin Psychopharmacol* 1995; **10:** 251–6.
4. Lapierre YD, *et al.* A Canadian multicenter study of three fixed doses of controlled-release ipsapirone in outpatients with moderate to severe major depression. *J Clin Psychopharmacol* 1998; **18:** 268–73.

Ketazolam *(BAN, USAN, rINN)*

Ketatsolaami; Kétazolam; Ketazolamum; U-28774. 11-Chloro-8,12b-dihydro-2,8-dimethyl-12b-phenyl-4*H*-[1,3]oxazino[3,2-*d*][1,4]benzodiazepine-4,7(6*H*)-dione.

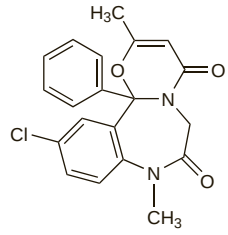
Кетазолам

$C_{20}H_{17}ClN_2O_3$ = 368.8.

CAS — 27223-35-4.

ATC — N05BA10.

ATC Vet — QN05BA10.



Profile

Ketazolam is a long-acting benzodiazepine with general properties similar to those of diazepam (p.986). It is given in the short-term treatment of anxiety (p.952) in usual oral doses of 15 to 60 mg daily, either in divided doses or as a single dose at night. Reduced doses may be required in elderly or debilitated patients.

◊ References.

1. Angelini G, *et al.* Ketazolam, a new long-acting benzodiazepine, in the treatment of anxious patients: a multicenter study of 2,056 patients. *Curr Ther Res* 1989; **45:** 294–304.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Ansieten; ***Belg.:*** Solatran†; ***Chile:*** Ansietil; Sedatival; ***Ital.:*** Anseren; ***Port.:*** Unakalm; ***S.Afr.:*** Solatran; ***Spain:*** Marcen; Sedotime; ***Switz.:*** Solatran.

Levomepromazine *(BAN, USAN, rINN)*

CL-36467; CL-39743; Levomepromatsiini; Levomepromazin; Levomepromazina; Lévomépromazine; Levomepromazinum; Methotrimeprazine; RP-7044; SKF-5116; XP-03. (–)-*NN*-Dimethyl-3-(2-methoxyphenothiazin-10-yl)-2-methylpropylamine; 3-(2-Methoxyphenothiazin-10-yl)-2-methylpropyldimethylamine.

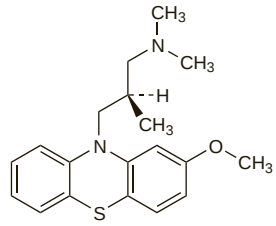
Левомепромазин

$C_{19}H_{24}N_2OS$ = 328.5.

CAS — 60-99-1.

ATC — N05AA02.

ATC Vet — QN05AA02.



Pharmacopoeias. In *US.* Also in *BP(Vet).*

BP(Vet) 2008 (Levomepromazine). A white or slightly cream-coloured crystalline powder. Practically insoluble in water; slightly soluble in alcohol; freely soluble in ether. Protect from light.

USP 31 (Methotrimeprazine). A fine white, practically odourless, crystalline powder. Soluble 1 in 10 of water, of alcohol, and of methyl alcohol, and 1 in 2 of chloroform; freely soluble in ether; sparingly soluble in alcohol at 25° but freely soluble in boiling alcohol. Store at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Levomepromazine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de levomepromazina; Levomepromatsiinihydrokloridi; Levomepromazin hydrochlorid; Lévomépromazine, chlorhydrate de; Levomepromazin-hidroklorid; Levomepromazinhydroklorid; Levomepromazini hydrochloridum; Levomepromazino hidrochloridas; Lewomepromazyny chlorowodorek; Methotrimeprazine Hydrochloride.

Левомепромазина Гидрохлорид

$C_{19}H_{24}N_2OS,HCl$ = 364.9.

CAS — 4185-80-2; 1236-99-3.

ATC — N05AA02.

ATC Vet — QN05AA02.

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

Ph. Eur. 6.2 (Levomepromazine Hydrochloride). A white or very slightly yellow, slightly hygroscopic crystalline powder. It deteriorates on exposure to air and light. Freely soluble in water and in alcohol. Store in airtight containers. Protect from light.

Incompatibility. Levomepromazine hydrochloride is reported to be incompatible with alkaline solutions.

Levomepromazine Maleate *(BANM, USAN, rINNM)*

Levomepromatsiinimaleaatti; Levomepromazin maleinát; Lévomépromazine, maléate de; Levomepromazini maleas; Levomepromazinmaleat; Levomepromazin-maleát; Levomepromazino maleatas; Lewomepromazyny maleinian; Maleato de levomepromazina; Methotrimeprazine Hydrogen Maleate; Methotrimeprazine Maleate.

Левомепромазина Малеат

$C_{19}H_{24}N_2OS,C_4H_4O_4$ = 444.5.

CAS — 7104-38-3.

ATC — N05AA02.

ATC Vet — QN05AA02.

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

Ph. Eur. 6.2 (Levomepromazine Maleate). A white or slightly yellowish crystalline powder. It deteriorates when exposed to air and light. Slightly soluble in water and in alcohol; sparingly soluble in dichloromethane. The supernatant of a 2% dispersion in water has a pH of 3.5 to 5.5. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p.969, although it may be more sedating. See also Adverse Effects of Antihistamines, p.561.

Levomepromazine may cause severe orthostatic hypotension, and patients taking large initial doses, patients over 50 years of age, or those given injections, should be lying down. Children are very susceptible to the hypotensive and sedative effects of levomepromazine.

Interactions

As for Chlorpromazine, p.973.

Antidepressants. Although *MAOIs* have been used with phenothiazines without untoward effects, the use of levomepromazine with MAOIs should probably be avoided as this combination has been implicated in 2 fatalities.[1,2]

1. Barsa JA, Saunders JC. A comparative study of tranylcypromine and pargyline. *Psychopharmacologia* 1964; **6:** 295–8.
2. McQueen EG. New Zealand committee on adverse drug reactions: fourteenth annual report 1979. *N Z Med J* 1980; **91:** 226–9.

Pharmacokinetics

◊ In a study involving 5 psychiatric patients peak plasma concentrations of levomepromazine were noted 1 to 4 hours after oral doses and 30 to 90 minutes after injection into the gluteal muscle.[1] About 50% of an oral dose reached the systemic circulation. Although the metabolite levomepromazine sulfoxide could not be detected after a single intramuscular injection, it was found in concentrations higher than unmetabolised levomepromazine after single and multiple oral dosage, both substances reaching a steady state in the plasma within 7 days of starting multiple-dose oral therapy. Fluctuations in plasma concentration during multiple-dose oral therapy indicated that until the correlation between acute adverse effects and peak plasma concentration of levomepromazine had been further studied the total daily dose should be divided into 2 or 3 portions when larger oral doses of levomepromazine are used.

1. Dahl SG. Pharmacokinetics of methotrimeprazine after single and multiple doses. *Clin Pharmacol Ther* 1976; **19:** 435–42.

Half-life. In 8 psychiatric patients given levomepromazine 50 to 350 mg daily the plasma half-life showed wide variation, from 16.5 to 77.8 hours, and did not correlate with the dose given.[1]

1. Dahl SG, *et al.* Pharmacokinetics and relative bioavailability of levomepromazine after repeated administration of tablets and syrup. *Eur J Clin Pharmacol* 1977; **11:** 305–310.

Uses and Administration

Levomepromazine is a phenothiazine with pharmacological activity similar to that of both chlorpromazine (p.975) and promethazine (p.589). It has antihistaminic actions (p.561) as well as CNS effects resembling those of chlorpromazine. It is also reported to have analgesic activity. It is used in the treatment of various psychoses including schizophrenia (p.955), as an analgesic for moderate to severe pain usually in non-ambulatory patients, and for premedication (p.1780). It is also used in palliative care for the control of symptoms such as restlessness, agitation, and as an adjunct to opioid analgesia, as well as being an effective broad-spectrum antiemetic in nausea and vomiting (p.1700).

Levomepromazine is also used in veterinary medicine.

Levomepromazine is given orally as the maleate or the hydrochloride or by injection as the hydrochloride. In the UK, doses such as those given below are expressed in terms of the appropriate salt. However, in some countries, the dose of levomepromazine may be expressed in terms of the base. The embonate has also been used. Care is required in elderly patients because of the risk of severe hypotension; if levomepromazine is given to such patients reduced doses may be necessary.

The usual initial oral dose of levomepromazine maleate for the treatment of **schizophrenia** is 25 to 50 mg daily; the daily dosage is usually divided into 3 portions with a larger portion taken at night. Doses of 100 to 200 mg have been given to non-ambulant patients increased gradually up to 1 g daily if necessary. Children are very susceptible to the hypotensive and sedative effects of levomepromazine: a suggested oral dose for a 10-year-old is 12.5 to 25 mg of the maleate daily in divided doses; a dose of 37.5 mg daily should not be exceeded.

When used in **palliative care** as an adjunct to analgesics in the management of severe terminal **pain** and for the control of **nausea and vomiting**, levomepromazine maleate may be given orally in a dose of 12.5 to 50 mg every 4 to 8 hours. The *BNF* also includes an oral dose of levomepromazine maleate 6 to 25 mg daily given in 1 or 2 divided doses for the management of nausea and vomiting where first-line antiemetics have proved inadequate. Alternatively 12.5 to 25 mg of levomepromazine hydrochloride may be given intramuscularly every 6 to 8 hours but patients should remain in bed for at least the first few doses; doses of up to 50 mg have been given for severe agitation. Levomepromazine hydrochloride may also be given intravenously in similar doses after dilution with an equal volume of sodium chloride 0.9% injection. Alternatively it may be given, suitably diluted with sodium chloride 0.9% injection, by continuous subcutaneous infusion via a syringe driver; doses range from a total of 25 to 200 mg daily although lower doses of 5 to 25 mg daily may also be effective against nausea and vomiting. Experience with parenteral use of levomepromazine hydrochloride in children is limited but a dose of 100 to 400 micrograms/kg daily by continuous intravenous or subcutaneous infusion has been suggested for children aged 1 month and over in the management of nausea and vomiting in palliative care; it has also been used in the treatment of restlessness and confusion in palliative care in a dose of 0.35 to 3 mg/kg daily by continuous subcutaneous infusion in those aged 1 year and over.

Levomepromazine hydrochloride given intramuscularly has been used in some countries for the control of acute pain, as a **premedicant**, and for postoperative analgesia. In some countries levomepromazine is also licensed for use as an **anxiolytic** and **sedative**, and in the management of other types of pain, including **labour pain**.

Pain. As levomepromazine appears to possess intrinsic analgesic activity in addition to its antiemetic and antipsychotic actions it has been used for the symptomatic control of restlessness and vomiting and as an adjunct to opioid analgesics in pain control (see Choice of Analgesic, p.2) in terminally ill patients.

References.

1. Oliver DJ. The use of methotrimeprazine in terminal care. *Br J Clin Pract* 1985; **39:** 339–40.
2. Patt RB, *et al.* The neuroleptics as adjuvant analgesics. *J Pain Symptom Manage* 1994; **9:** 446–53.
3. O'Neill J, Fountain A. Levomepromazine (methotrimeprazine) and the last 48 hours. *Hosp Med* 1999; **60:** 564–7.
4. Skinner J, Skinner A. Levomepromazine for nausea and vomiting in advanced cancer. *Hosp Med* 1999; **60:** 568–70.

HEADACHE. Levomepromazine is one of those phenothiazines (see p.976) that has been effective[1] in relieving the pain of severe migraine attacks.

1. Stiell IG, *et al.* Methotrimeprazine versus meperidine and dimenhydrinate in the treatment of severe migraine: a randomized, controlled trial. *Ann Emerg Med* 1991; **20:** 1201–5.

Preparations

BP 2008: Levomepromazine Injection; Levomepromazine Tablets; ***USP 31:*** Methotrimeprazine Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Detenler; Levolam; Nozinan; Togrel; ***Austria:*** Nozinan; ***Belg.:*** Nozinan; ***Braz.:*** Levozine; Neozine; ***Canad.:*** Apo-Methoprazine; Novo-Mepraz ine†; Nozinan; ***Chile:*** Sinogan; ***Cz.:*** Tisercin; ***Denm.:*** Nozinan; ***Fin.:*** Levozin; Nozinan; ***Fr.:*** Nozinan; ***Ger.:*** Levium; Neurocil; ***Gr.:*** Nozinan; Prazine†; Sinogan; ***Hung.:*** Tisercin; ***Irl.:*** Nozinan; ***Israel:*** Methozane; Nozinan; Ronexine; ***Ital.:*** Nozinan; ***Mex.:*** Levocina; Sinogan; ***Neth.:*** Nozinan; ***Norw.:*** Nozinan; ***NZ:*** Nozinan; ***Philipp.:*** Nozinan; ***Pol.:*** Tisercin; ***Port.:*** Nozinan; ***Rus.:*** Tisercin (Тизерцин); ***Spain:*** Sinogan; ***Swed.:*** Nozinan; ***Switz.:*** Nozinan; ***UK:*** Levinan; Nozinan; ***Venez.:*** Sinogan.

Loprazolam Mesilate *(BANM, rINNM)*

HR-158; Loprazolam, Mésilate de; Loprazolam Mesylate; Loprazolam Methanesulphonate; Loprazolami Mesilas; Mesilato de loprazolam; RU-31158. 6-(2-Chlorophenyl)-2,4-dihydro-2-(4-methylpiperazin-1-ylmethylene)-8-nitroimidazo[1,2-*a*][1,4]benzodiazepin-1-one methanesulphonate monohydrate.

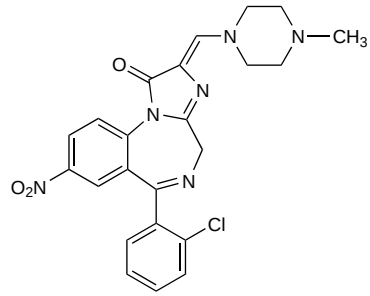
Лопразолама Мезилат

$C_{23}H_{21}ClN_6O_3,CH_4O_3S,H_2O$ = 579.0.

CAS — 61197-73-7 (loprazolam); 70111-54-5 (anhydrous loprazolam mesilate).

ATC — N05CD11.

ATC Vet — QN05CD11.



(loprazolam)

Pharmacopoeias. In *Br.*

BP 2008 (Loprazolam Mesilate). A yellow crystalline powder. Slightly soluble in water, in alcohol, and in chloroform; very slightly soluble in ether.

Dependence and Withdrawal

As for Diazepam, p.987.

◊ For the purpose of withdrawal regimens, 0.5 to 1 mg of loprazolam is considered equivalent to about 5 mg of diazepam.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p.987.

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

Interactions

As for Diazepam, p.989.

Pharmacokinetics

◊ References.

1. Garzone PD, Kroboth PD. Pharmacokinetics of the newer benzodiazepines. *Clin Pharmacokinet* 1989; **16:** 337–64.
2. Dorling MC, Hindmarch I. Pharmacokinetic profile of loprazolam in 12 young and 12 elderly healthy volunteers. *Drugs Exp Clin Res* 2001; **27:** 151–9.

Uses and Administration

Loprazolam is an intermediate-acting benzodiazepine with general properties similar to those of diazepam (p.992).

Loprazolam mesilate is usually used for its hypnotic properties in the short-term management of insomnia (p.957), in usual oral doses equivalent to 1 mg of loprazolam at night. Dosage may be increased to up to 2 mg if necessary. A starting dose of 0.5 mg increased to a maximum of 1 mg may be appropriate for elderly or debilitated patients.

Preparations

BP 2008: Loprazolam Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Dormonoct; ***Belg.:*** Dormonoct; ***Fr.:*** Havlane; ***Ger.:*** Sonin; ***Neth.:*** Dormonoct; ***Port.:*** Dormonoct; ***S.Afr.:*** Dormonoct; ***Spain:*** Somnovit.