6. Timmer CJ, Sitsen JM. Pharmacokinetic evaluation of gepirone immediate-release capsules and gepirone extended-release tablets in healthy volunteers. *J Pharm Sci* 2003; **92:** 1773–8.
7. Amsterdam JD, *et al.* Sustained efficacy of gepirone-IR in major depressive disorder: a double-blind placebo substitution trial. *J Psychiatr Res* 2004; **38:** 259–65.
8. Alpert JE, *et al.* Gepirone extended-release treatment of anxious depression: evidence from a retrospective subgroup analysis in patients with major depressive disorder. *J Clin Psychiatry* 2004; **65:** 1069–75.
9. Keller MB, *et al.* Relapse prevention with gepirone ER in outpatients with major depression. *J Clin Psychopharmacol* 2005; **25:** 79–84.

Glutethimide *(BAN, rINN)*

Glutéthimide; Glutethimidum; Glutetimid; Glutetimida; Glutetimide; Glutetimidi. 2-Ethyl-2-phenylglutarimide; 3-Ethyl-3-phenylpiperidine-2,6-dione.

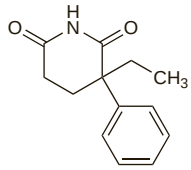
Глутетимид

$C_{13}H_{15}NO_2$ = 217.3.

CAS — 77-21-4.

ATC — N05CE01.

ATC Vet — QN05CE01.



NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of glutethimide: CIBAs; D; Doors; Goofers.

Profile

Glutethimide is a piperidinedione hypnotic and sedative with effects broadly similar to those of the barbiturates (see Amobarbital, p.961). It also has antimuscarinic properties. It has been given for the short-term management of insomnia but it has been superseded by other drugs.

Abuse. A warning of the hazards associated with the abuse of glutethimide in a combination with codeine termed 'loads'.[1]

1. Sramek JJ, Khajawall A. "Loads". *N Engl J Med* 1981; **305:** 231.

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

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Hung.:*** Tardyl†.

Halazepam *(BAN, USAN, rINN)*

Halatsepaami; Halazépam; Halazepamum; Sch-12041. 7-Chloro-1,3-dihydro-5-phenyl-1-(2,2,2-trifluoroethyl)-1,4-benzodiazepin-2-one.

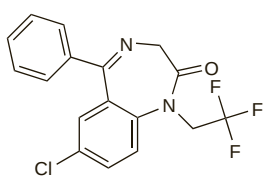
Галазепам

$C_{17}H_{12}ClF_3N_2O$ = 352.7.

CAS — 23092-17-3.

ATC — N05BA13.

ATC Vet — QN05BA13.



Profile

Halazepam is a benzodiazepine with general properties similar to those of diazepam (p.986). It has been given for the short-term treatment of anxiety disorders (p.952) in usual oral doses of 20 to 40 mg every 6 to 8 hours.

Preparations

Proprietary Preparations (details are given in Part 3)

Port.: Pacinone; ***Spain:*** Alapryl.

Haloperidol *(BAN, USAN, rINN)*

Aloperidolo; Halopéridol; Haloperidoli; Haloperidolis; Haloperidolum; McN-JR-1625; R-1625. 4-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-4′-fluorobutyrophenone.

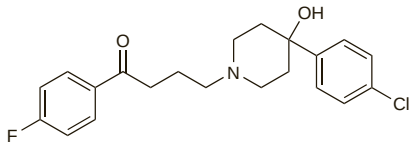
Галоперидол

$C_{21}H_{23}ClFNO_2$ = 375.9.

CAS — 52-86-8.

ATC — N05AD01.

ATC Vet — QN05AD01.



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

Ph. Eur. 6.2 (Haloperidol). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol, in dichloromethane, and in methyl alcohol. Protect from light.

USP 31 (Haloperidol). A white to faintly yellowish amorphous or microcrystalline powder. Practically insoluble in water; soluble 1 in 60 of alcohol, 1 in 15 of chloroform, and 1 in 200 of ether. A saturated solution is neutral to litmus. Store in airtight containers. Protect from light.

Dilution. See Incompatibility, below.

Incompatibility. A precipitate formed after dilution of haloperidol (as the lactate) in sodium chloride 0.9% injection when the final haloperidol concentration was 1 mg/mL or higher.[1]

Undiluted haloperidol (5 mg/mL) injection has been reported to be incompatible with heparin sodium (diluted in sodium chloride 0.9% or glucose 5% injection),[2] sodium nitroprusside (diluted in glucose 5%),[1] cefmetazole sodium,[3] and diphenhydramine.[4] A mixture of equal volumes of sargramostim 10 micrograms/mL and haloperidol (as the lactate) 200 micrograms/mL resulted in a precipitate at 4 hours.[5]

1. Outman WR, Monolakis J. Visual compatibility of haloperidol lactate with 0.9% sodium chloride injection or injectable critical-care drugs during simulated Y-site injection. *Am J Hosp Pharm* 1991; **48:** 1539–41.
2. Solomon DA, Nasinnyk KK. Compatibility of haloperidol lactate and heparin sodium. *Am J Hosp Pharm* 1982; **39:** 843–4.
3. Hutchings SR, *et al.* Compatibility of cefmetazole sodium with commonly used drugs during Y-site delivery. *Am J Health-Syst Pharm* 1996; **53:** 2185–8.
4. Ukhun IA. Compatibility of haloperidol and diphenhydramine in a hypodermic syringe. *Ann Pharmacother* 1995; **29:** 1168–9.
5. Trissel LA, *et al.* Visual compatibility of sargramostim with selected antineoplastic agents, anti-infectives, or other drugs during simulated Y-site injection. *Am J Hosp Pharm* 1992; **49:** 402–6.

Stability. A combination of the stabilisers benzyl alcohol and vanillin could protect haloperidol from photodegradation.[1]

1. Thoma K, Klimek R. Photostabilisation of drugs in dosage forms without protection from packaging materials. *Int J Pharmaceutics* 1991; **67:** 169–75.

Haloperidol Decanoate *(BANM, USAN, rINNM)*

Decanoato de haloperidol; Halopéridol, décanoate d'; Haloperidoldekanoat; Haloperidol-dekanoát; Haloperidoli decanoas; Haloperidolidekanoaatti; Haloperidolio dekanoatas; R-13672.

Галоперидола Деканоат

$C_{31}H_{41}ClFNO_3$ = 530.1.

CAS — 74050-97-8.

ATC — N05AD01.

ATC Vet — QN05AD01.

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

Ph. Eur. 6.2 (Haloperidol Decanoate). A white or almost white powder. It melts at about 42°. Practically insoluble in water; very soluble in alcohol, in dichloromethane, and in methyl alcohol. Store at a temperature below 25°. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p.969. Haloperidol is less likely to cause sedation, hypotension, or antimuscarinic effects, but is associated with a higher incidence of extrapyramidal effects. Haloperidol should be used with great care in children and adolescents as they may be at increased risk of severe dystonic reactions; patients with hyperthyroidism may also be at increased risk.

Breast feeding. The American Academy of Pediatrics[1] considers that the use of haloperidol by mothers during breast feeding may be of concern, since there have been reports of decline in developmental scores in breast-fed infants. Licensed product information also reports that there have been isolated cases of extrapyramidal effects in breast-fed infants.

The concentration of haloperidol in breast milk of one mother given a mean daily dose of about 30 mg for 6 days was reported to be 5 nanograms/mL; on day 12 the concentration 9 hours after a 12-mg dose was 2 nanograms/mL.[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. Stewart RB, *et al.* Haloperidol excretion in human milk. *Am J Psychiatry* 1980; **137:** 849–50.

Convulsions. For mention of haloperidol as one of the antipsychotics suitable for patients at risk of seizures, see p.969.

Effects on the liver. Liver dysfunction with jaundice and eosinophilia developed in a 15-year-old male 4 weeks after starting haloperidol and benzatropine mesilate.[1] The drugs were stopped 2 weeks later but some symptoms lasted for 28 months. The reaction was suggestive of a drug-induced hypersensitivity reaction and haloperidol was the most likely cause. Haloperidol-induced liver injury was considered to be rare.

1. Dincsoy HP, Saelinger DA. Haloperidol-induced chronic cholestatic liver disease. *Gastroenterology* 1982; **83:** 694–700.

Overdosage. Symptoms of haloperidol overdosage in children have ranged from the expected, such as drowsiness, restlessness, confusion, marked extrapyramidal symptoms, and hypothermia,[1,2] to unexpected reactions such as bradycardia (possibly secondary to hypothermia)[1] and an episode of severe, delayed hypertension.[3]

Torsade de pointes has followed overdosage in adults (for references, see Effects on the Cardiovascular System under Chlorpromazine, p.970).

1. Scialli JVK, Thornton WE. Toxic reactions from a haloperidol overdose in two children: thermal and cardiac manifestations. *JAMA* 1978; **239:** 48–9.
2. Sinaniotis CA, *et al.* Acute haloperidol poisoning in children. *J Pediatr* 1978; **93:** 1038–9.
3. Cummingham DG, Challapalli M. Hypertension in acute haloperidol poisoning. *J Pediatr* 1979; **95:** 489–90.

Porphyria. Haloperidol is considered to be unsafe in patients with porphyria although there is conflicting experimental evidence of porphyrinogenicity.

Retroperitoneal fibrosis. Obstructive uropathy was noted in a 45-year-old woman given haloperidol 5 to 15 mg daily for 8 years.[1] Benzatropine was also taken during that time, and in the previous 5 years she had taken chlorpromazine and fluphenazine. A diagnosis of retroperitoneal fibrosis was made and was tentatively associated with long-term antipsychotic therapy.

1. Jeffries JJ, *et al.* Retroperitoneal fibrosis and haloperidol. *Am J Psychiatry* 1982; **139:** 1524–5.

Toxic encephalopathy. A report[1] of possible toxic encephalopathy after use of high intravenous doses of haloperidol. The patient, who had a history of bipolar disorder and cerebrovascular accident, had been given increasing intravenous doses of haloperidol (up to 270 mg daily) to control post-surgical agitation. The encephalopathy had resolved 8 days after stopping haloperidol.

1. Maxa JL, *et al.* Possible toxic encephalopathy following high-dose intravenous haloperidol. *Ann Pharmacother* 1997; **31:** 736–7.

Interactions

As for Chlorpromazine, p.973.

Haloperidol must be used with extreme caution in patients receiving lithium; an encephalopathic syndrome has been reported after their use together (see p.405).

Pharmacokinetics

Haloperidol is readily absorbed from the gastrointestinal tract. It is metabolised in the liver and is excreted in the urine and, via the bile, in the faeces; there is evidence of enterohepatic recycling. Owing to first-pass metabolism in the liver, plasma concentrations after oral doses are lower than those after intramuscular injection. Moreover, there is wide intersubject variation in plasma concentrations of haloperidol. In practice, however, no strong correlation has been found between plasma concentrations of haloperidol and its therapeutic effect. Paths of metabolism of haloperidol include oxidative *N*-dealkylation and reduction of the ketone group to form an alcohol known as reduced haloperidol. Haloperidol has been reported to have a plasma elimination half-life ranging from about 12 to 38 hours after oral doses. Haloperidol is about 92% bound to plasma proteins. It is widely distributed in the body and crosses the blood-brain barrier. Haloperidol is distributed into breast milk.