Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Hung.:*** Demalgon.

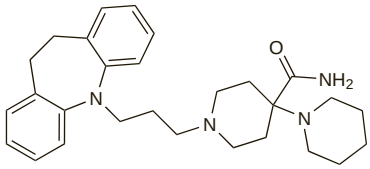
Carpipramine Hydrochloride *(rINNM)*

Carpipramine, Chlorhydrate de; Carpipramini Hydrochloridum; Hidrocloruro de carpipramina; PZ-1511. 1-[3-(10,11-Dihydro-5*H*-dibenz[*b,f*]azepin-5-yl)propyl]-4-piperidinopiperidine-4-carboxamide dihydrochloride monohydrate.

Карпипрамина Гидрохлорид

$C_{28}H_{38}N_4O,2HCl,H_2O$ = 537.6.

CAS — 5942-95-0 (carpipramine); 7075-03-8 (anhydrous carpipramine hydrochloride).



(carpipramine)

Profile

Carpipramine is structurally related both to imipramine (p.400) and to butyrophenones such as haloperidol (p.1000). It has been used in the management of anxiety disorders (p.952) and psychoses such as schizophrenia (p.955). Carpipramine is given as the hydrochloride although doses are expressed in terms of the base; carpipramine hydrochloride 60.2 mg is equivalent to about 50 mg of carpipramine. A usual oral dose is equivalent to 150 mg of the base daily in 2 or 3 divided doses, with a range of 50 to 400 mg daily.

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

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Prazinil.

Chlordiazepoxide *(BAN, rINN)*

Chlordiazepoksidas; Chlordiazepoxid; Chlordiazépoxide; Chlordiazepoxidum; Chlorodiazepoksyd; Clordiazepóxido; Klooridiatsepoksidi; Klordiazepoksit; Klórdiazepoxid; Klordiazepoxid; Methaminodiazepoxide. 7-Chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide.

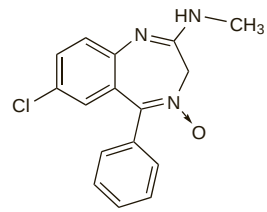
Хлордиазепоксид

$C_{16}H_{14}ClN_3O$ = 299.8.

CAS — 58-25-3.

ATC — N05BA02.

ATC Vet — QN05BA02.



NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of chlordiazepoxide: Lib.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn*, and *US*.
Ph. Eur. 6.2 (Chlordiazepoxide). An almost white or light yellow, crystalline powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol. Protect from light.
USP 31 (Chlordiazepoxide). A yellow, practically odourless, crystalline powder. Insoluble in water; soluble 1 in 50 of alcohol, 1 in 6250 of chloroform, and 1 in 130 of ether. Store in airtight containers. Protect from light.

Chlordiazepoxide Hydrochloride *(BANM, USAN, rINNM)*

Chlordiazepoksido hidrochloridas; Chlordiazepoksydu chlorowodorek; Chlordiazépoxide, chlorhydrate de; Chlordiazepoxidhydrochlorid; Chlordiazepoxidi hydrochloridum; Hidrocloruro de clordiazepóxido; Klooridiatsepoksidihydrokloridi; Klordiazepoksit Hidroklorür; Klórdiazepoxid-hidroklorid; Klordiazepoxidhydroklorid; Methaminodiazepoxide Hydrochloride; NSC-115748; Ro-5-0690.

Хлордиазепоксида Гидрохлорид

$C_{16}H_{14}ClN_3O,HCl$ = 336.2.
CAS — 438-41-5.
ATC — N05BA02.
ATC Vet — QN05BA02.

Pharmacopoeias. In *Eur.* (see p.vii) and *US*.
Ph. Eur. 6.2 (Chlordiazepoxide Hydrochloride). A white or slightly yellow, crystalline powder. It exhibits polymorphism. Soluble in water; sparingly soluble in alcohol. Protect from light.
USP 31 (Chlordiazepoxide Hydrochloride). A white or practically white, odourless, crystalline powder. Soluble in water; sparingly soluble in alcohol; insoluble in petroleum spirit. Store in airtight containers. Protect from light.

Dependence and Withdrawal

As for Diazepam, p.987.

◊ For the purpose of withdrawal regimens, 15 mg of chlordiazepoxide is considered equivalent to about 5 mg of diazepam.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p.987.

Hepatic impairment. Progressive drowsiness began after 20 days of treatment with chlordiazepoxide in a woman with cirrhosis and hepatitis.[1] One week after stopping the drug the patient could not be roused, and full consciousness was not regained for another week. Accumulation of active metabolites of chlordiazepoxide may have been responsible for the prolonged stupor.

1. Barton K, *et al*. Chlordiazepoxide metabolite accumulation in liver disease. *Med Toxicol* 1989; **4:** 73–6.

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

Interactions

As for Diazepam, p.989.

Pharmacokinetics

Absorption of chlordiazepoxide is almost complete after oral doses; peak plasma concentrations are achieved after 1 to 2 hours. Absorption after intramuscular injection may be slow and erratic depending on the site of injection. Chlordiazepoxide is about 96% bound to plasma proteins. Reported values for the elimination half-life of chlordiazepoxide have ranged from about 5 to 30 hours, but its main active metabolite desmethyldiazepam (nordazepam, p.1012) has a half-life of several days. Other pharmacologically active metabolites of chlordiazepoxide include desmethylchlordiazepoxide, demoxepam, and oxazepam (p.1014). Chlordiazepoxide passes into the CSF and breast milk, and crosses the placenta. Unchanged drug and metabolites are excreted in the urine, mainly as conjugated metabolites.

◊ References.

1. Greenblatt DJ, *et al*. Clinical pharmacokinetics of chlordiazepoxide. *Clin Pharmacokinet* 1978; **3:** 381–94.

Uses and Administration

Chlordiazepoxide is a benzodiazepine with general properties similar to those of diazepam (p.992). It is used in the short-term treatment of anxiety disorders (p.952) and insomnia (p.957). Chlordiazepoxide is also used in muscle spasm (p.1887), in alcohol withdrawal syndrome (p.1626), and for premedication (p.1780).

Chlordiazepoxide is given orally as the hydrochloride or the base; the doses given refer equally to both. It may also be given by deep intramuscular or slow intravenous injection as the hydrochloride. Preparations formulated for intramuscular use are considered unsuitable for intravenous injection due to the formation of air bubbles in the solvent.

Elderly and debilitated patients should be given one-half or less of the usual adult dose.

The usual oral dose for the treatment of **anxiety** is up to 30 mg daily in divided doses; in severe conditions up to 100 mg daily has been given. For acute or severe anxiety an initial dose of 50 to 100 mg of the hydrochloride has been given by injection, followed if necessary by 25 to 50 mg three or four times daily.

For relief of **muscle spasm** a dose of 10 to 30 mg daily orally in divided doses is recommended, and 10 to 30 mg orally may be given before bedtime for insomnia associated with anxiety.

For the control of the acute symptoms of **alcohol withdrawal** chlordiazepoxide or chlordiazepoxide hydrochloride may be given in an oral dose of 25 to 100 mg repeated as needed up to a maximum of 300 mg daily. For severe symptoms treatment may be begun by injection of 50 to 100 mg, repeated if necessary after 2 to 4 hours.

Chlordiazepoxide hydrochloride has also been given for anaesthetic **premedication** in a dose of 50 to 100 mg intramuscularly one hour before surgery.

Preparations

BP 2008: Chlordiazepoxide Capsules; Chlordiazepoxide Hydrochloride Tablets;
USP 31: Chlordiazepoxide and Amitriptyline Hydrochloride Tablets; Chlordiazepoxide Hydrochloride and Clidinium Bromide Capsules; Chlordiazepoxide Hydrochloride Capsules; Chlordiazepoxide Hydrochloride for Injection; Chlordiazepoxide Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: OCM; ***Braz.:*** Psicosedin; ***Cz.:*** Defobin†; Elenium; ***Denm.:*** Klopoxid; Risolid; ***Fin.:*** Risolid; ***Ger.:*** Librium; Multum; Radepur; ***Gr.:*** Oasil; ***Hong Kong:*** Librium; ***Hung.:*** Elenium; Librium; ***India:*** Equilibrium; Librium; ***Indon.:*** Cetabrium; Librium; ***Irl.:*** Librium; ***Ital.:*** Librium; Reliberan†; ***Malaysia:*** Benpine; Klorpo†; ***Mex.:*** Kalmocaps†; ***NZ:*** Novapam; ***Pol.:*** Elenium; ***Port.:*** Paxium; ***Rus.:*** Elenium (Элениум); ***S.Afr.:*** Librium; ***Singapore:*** Benpine; Klorpo; ***Spain:*** Huberplex; Omnalio; ***Thai.:*** Benpine; Cozep; Epoxide†; ***UK:*** Librium; Tropium; ***USA:*** Libritabs†; Librium; Mitran†; Reposans†; ***Venez.:*** Eposal.

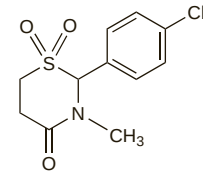
Multi-ingredient: ***Arg.:*** Libraxin; Plafonyl†; ***Austria:*** Limbitrol; ***Braz.:*** Limbitrol; Menotensil; ***Canad.:*** Apo-Chlorax; Librax; ***Chile:*** Aero Itan; Aerogastrol; Antalin; Garceptol; Gaseofin†; Gastrolen; Lerogin; Libraxin; Limbatrilin; Lironex†; Morelin; No-Ref; Profisin; Sedogastrol†; Tensoliv; Tiperin; Tranvagal†; ***Fin.:*** Klotriptyl; Librax; Limbitrol; ***Fr.:*** Librax; ***Gr.:*** Librax; ***Hong Kong:*** Bralix; Epilon; Librax; Medocalum†; ***India:*** Emotrip; Equirex; Normaxin; Spasrax; ***Indon.:*** Braxidin; Cliad; Klidibrax; Librax; Limbritol; Melidox; Neurogen; Renagas; Sanmag; Spasmium; ***Israel:*** Nirvaxal; ***Ital.:*** Diapatol; Librax; Limbitryl; Sedans; ***Malaysia:*** Apo-Chlorax†; Liblan; ***Port.:*** Librax; ***Rus.:*** Amixide (Амиксид); ***S.Afr.:*** Librax; Limbitrol; ***Singapore:*** Apo-Chlorax; Chlobax; Librax; Medocalum; ***Spain:*** Psico Blocan; ***Switz.:*** Librax; Librocol; Limbitrol; ***Thai.:*** Kenspa; Librax; Pobrax†; Tumax; Zepobrax†; ***Turk.:*** Klipaks; Libkol; Librax; ***USA:*** Clindex; Librax; Limbitrol; ***Venez.:*** Librax.

Chlormezanone *(BAN, rINN)*

Chlormethazanone; Chlormézanone; Chlormezanonum; Clormezanona; Kloorimetsanoni; Klormezanon. 2-(4-Chlorophenyl)-3-methylperhydro-1,3-thiazin-4-one 1,1-dioxide.

Хлормезанон

$C_{11}H_{12}ClNO_3S$ = 273.7.
CAS — 80-77-3.
ATC — M03BB02.
ATC Vet — QM03BB02.



Profile

Chlormezanone has been used in the treatment of anxiety disorders and insomnia. It was also used in conditions associated with painful muscle spasm, often in compound preparations with analgesics; its mechanism of action is not clear but is probably related to its sedative effect. Chlormezanone was withdrawn from use in many countries after reports of serious skin reactions (see below).

Effects on the skin. Chlormezanone was responsible for 5 of 86 cases of fixed drug eruption detected in a Finnish hospital from 1971 to 1980.[1] In the period from 1981 to 1985 chlormezanone was responsible for 1 out of 77 such eruptions.[2] In a case control study[3] comparing drug use in 245 patients hospitalised because of toxic epidermal necrolysis or Stevens-Johnson syndrome and 1147 controls, 13 patients and one control were found to have taken chlormezanone. From these figures a high crude relative risk of 62 was calculated; the excess risk was estimated to be 1.7 cases per million users per week.

1. Kauppinen K, Stubb S. Fixed eruptions: causative drugs and challenge tests. *Br J Dermatol* 1985; **112:** 575–8.

2. Stubb S, *et al.* Fixed drug eruptions: 77 cases from 1981 to 1985. *Br J Dermatol* 1989; **120:** 583.
3. Roujeau J-C, *et al.* Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med* 1995; **333:** 1600–7.

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

Preparations

Proprietary Preparations (details are given in Part 3)
Chile: Cardiosedantol; Restoril†.

Multi-ingredient: ***Chile:*** Adalgen†; Calmosedan; Diapam; Dioran†; Dolnix; Dolonase; Dolorelax†; Fibrorelax; Mesolona†; Multisedil; Neo Butartrol; Promidan; Sedantol; Sedilit; Silrelax†; Sin-Algin; ***Hong Kong:*** Parazone; ***S.Afr.:*** Myoflex.

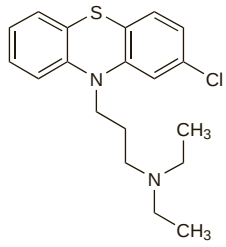
Chlorproethazine Hydrochloride *(rINNM)*

Chlorproéthazine, Chlorhydrate de; Chlorproethazini Hydrochloridum; Hidrocloruro de clorproetazina; RP-4909 (chlorproethazine). 3-(2-Chlorophenothiazin-10-yl)-*NN*-diethylpropylamine hydrochloride.

Хлорпроэтазина Гидрохлорид

$C_{19}H_{23}ClN_2S,HCl$ = 383.4.

CAS — 84-01-5 (chlorproethazine); 4611-02-3 (chlorproethazine hydrochloride).
ATC — N05AA07.
ATC Vet — QN05AA07.



(chlorproethazine)

Profile

Chlorproethazine is a phenothiazine derivative differing chemically from chlorpromazine by the substitution of a diethyl for a dimethyl group. It has general properties similar to those of chlorpromazine (below) but has been used mainly as a muscle relaxant in the management of muscle spasm (p.1887). Although exposure of the skin to phenothiazines has been associated with sensitivity reactions, chlorproethazine hydrochloride has been applied topically with the warning to avoid direct exposure to sunlight. It has also been given orally or by intramuscular or slow intravenous injection.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Neuriplege†.

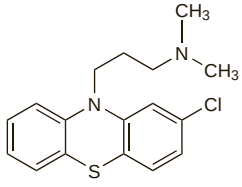
Chlorpromazine *(BAN, rINN)*

Chlorpromazinum; Clorpromazina; Klooripromatsiini; Klorpromazin. 3-(2-Chlorophenothiazin-10-yl)propyldimethylamine.

Хлорпромазин

$C_{17}H_{19}ClN_2S$ = 318.9.

CAS — 50-53-3.
ATC — N05AA01.
ATC Vet — QN05AA01.



Pharmacopoeias. In *Br.* and *US*.

BP 2008 (Chlorpromazine). A white or creamy-white powder or waxy solid; odourless or almost odourless. M.p. 56° to 58°. Practically insoluble in water; freely soluble in alcohol and in ether; very soluble in chloroform. Protect from light.

USP 31 (Chlorpromazine). A white crystalline solid with an amine-like odour. It darkens on prolonged exposure to light. Practically insoluble in water; soluble 1 in 3 of alcohol, 1 in 2 of chloroform, 1 in 3 of ether, and 1 in 2 of benzene; freely soluble in dilute mineral acids; practically insoluble in dilute alkali hydroxides. Store in airtight containers. Protect from light.

Chlorpromazine Embonate *(BANM, rINNM)*

Chlorpromazine, Embonate de; Chlorpromazine Pamoate; Chlorpromazini Embonas; Embonato de clorpromazina.

Хлорпромазина Эмбонат

$(C_{17}H_{19}ClN_2S)_2,C_{23}H_{16}O_6$ = 1026.1.

ATC — N05AA01.
ATC Vet — QN05AA01.

Chlorpromazine Hydrochloride *(BANM, rINNM)*

Aminazine; Chloropromazyny chlorowodorek; Chlorpromazin hydrochlorid; Chlorpromazine, chlorhydrate de; Chlorpromazini hydrochloridum; Chlorpromazino hidrochloridas; Hidrocloruro de clorpromazina; Klooripromatsiinihydrokloridi; Klorpromazin Hidroklorür; Klórpromazin-hidroklorid; Klorpromazinhydroklorid.

Хлорпромазина Гидрохлорид

$C_{17}H_{19}ClN_2S,HCl$ = 355.3.

CAS — 69-09-0.
ATC — N05AA01.
ATC Vet — QN05AA01.

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

Ph. Eur. 6.2 (Chlorpromazine Hydrochloride). A white or almost white crystalline powder. It decomposes on exposure to air and light. Very soluble in water; freely soluble in alcohol. A freshly prepared 10% solution in water has a pH of 3.5 to 4.5. Store in airtight containers. Protect from light.

USP 31 (Chlorpromazine Hydrochloride). A white or slightly creamy-white odourless crystalline powder. It darkens on prolonged exposure to light. Soluble 1 in 1 of water, 1 in 1.5 of alcohol, and 1 in 1.5 of chloroform; insoluble in ether and in benzene. Store in airtight containers. Protect from light.

Dilution. Solutions containing 2.5% of chlorpromazine hydrochloride may be diluted to 100 mL with 0.9% sodium chloride solution provided the pH of the saline solution is such that the pH of the dilution does not exceed the critical range of pH 6.7 to 6.8.[1] With saline of pH 7.0 or 7.2, the final solution had a pH of 6.4.

1. D'Arcy PF, Thompson KM. Stability of chlorpromazine hydrochloride added to intravenous infusion fluids. *Pharm J* 1973; **210:** 28.

Incompatibility. Incompatibility has been reported between chlorpromazine hydrochloride injection and several other compounds; precipitation of chlorpromazine base from solution is particularly likely if the final pH is increased. Compounds reported to be incompatible with chlorpromazine hydrochloride include aminophylline, amphotericin B, aztreonam, some barbiturates, chloramphenicol sodium succinate, chlorothiazide sodium, dimenhydrinate, heparin sodium, morphine sulfate (when preserved with chlorocresol), some penicillins, and remifentanil.

For a warning about incompatibility between chlorpromazine solution (*Thorazine*; *GSK, USA*) and carbamazepine suspension (*Tegretol*; *Novartis, USA*), see p.471.

Sorption. There was a 41% loss of chlorpromazine hydrochloride from solution when infused for 7 hours via a plastic infusion set (cellulose propionate burette with PVC tubing), and a 79% loss after infusion for 1 hour from a glass syringe through silastic tubing.[1] Loss was negligible after infusion for 1 hour from a system comprising a glass syringe with polyethylene tubing.

1. Kowaluk EA, *et al.* Interactions between drugs and intravenous delivery systems. *Am J Hosp Pharm* 1982; **39:** 460–7.

Adverse Effects

Chlorpromazine generally produces less central depression than the barbiturates or benzodiazepines, and tolerance to its initial sedative effects develops fairly quickly in most patients. It has antimuscarinic properties and may cause adverse effects such as dry mouth, constipation, difficulty with micturition, blurred vision, and mydriasis. Tachycardia, ECG changes (particularly Q- and T-wave abnormalities), and, rarely, cardiac arrhythmias may occur; hypotension (usually orthostatic) is common. Other adverse effects include delirium, agitation and, rarely, catatonic-like states, insomnia or drowsiness, nightmares, depression, miosis, EEG changes and convulsions, nasal congestion, minor abnormalities in liver function tests, inhibition of ejaculation, impotence, and priapism.

Hypersensitivity reactions include urticaria, exfoliative dermatitis, erythema multiforme, and contact sensitivity. A syndrome resembling SLE has been reported. Jaundice has occurred, and probably has an immunological origin. Prolonged therapy may lead to deposition of pigment in the skin, or more frequently the eyes; corneal and lens opacities have occurred. Pigmentary retinopathy has occurred only rarely with chlorpromazine. Photosensitivity reactions are more common with chlorpromazine than with other antipsychotics.

Haematological disorders, including haemolytic anaemia, aplastic anaemia, thrombocytopenic purpura, eosinophilia, and a potentially fatal agranulocytosis have occasionally been reported; they may be manifestations of a hypersensitivity reaction. Most cases of agranulocytosis have occurred within 4 to 10 weeks of starting treatment, and symptoms such as sore throat or fever should be watched for and white cell counts instituted should they appear. Mild leucopenia has been stated to occur in up to 30% of patients on prolonged high dosage.

Extrapyramidal dysfunction and resultant disorders include acute dystonia, a parkinsonism-like syndrome, and akathisia; late effects include tardive dyskinesia and perioral tremor. The neuroleptic malignant syndrome may also occur.

Chlorpromazine alters endocrine and metabolic functions. Patients have experienced amenorrhoea, galactorrhoea, and gynaecomastia due to hyperprolactinaemia, weight gain, and hyperglycaemia and altered glucose tolerance. Body temperature regulation is impaired and may result in hypo- or hyperthermia depending on environment. There have also been reports of hypercholesterolaemia.

There have been isolated reports of sudden death with chlorpromazine; possible causes include cardiac arrhythmias or aspiration and asphyxia due to suppression of the cough and gag reflexes.

Pain and irritation at the injection site may occur on injection. Nodule formation may occur after intramuscular injection.

Phenothiazines do not cause dependence of the type encountered with barbiturates or benzodiazepines. However, withdrawal symptoms have been seen on abrupt withdrawal in patients receiving prolonged and/or high-dose maintenance therapy.

Although the adverse effects of **other phenothiazines** are broadly similar in nature to those of chlorpromazine, their frequency and pattern tend to fall into 3 groups:

- group 1 (e.g. chlorpromazine, levomepromazine, and promazine) are generally characterised by pronounced sedative effects and moderate antimuscarinic and extrapyramidal effects
- group 2 (e.g. pericyazine, pipotiazine, and thioridazine) are generally characterised by moderate sedative effects, marked antimuscarinic effects, and fewer extrapyramidal effects than groups 1 or 3
- group 3 (e.g. fluphenazine, perphenazine, prochlorperazine, and trifluoperazine) are generally characterised by fewer sedative and antimuscarinic effects but more pronounced extrapyramidal effects than groups 1 or 2

Classical antipsychotics of **other chemical groups** tend to resemble the phenothiazines of group 3. They include the butyrophenones (e.g. benperidol and haloperidol); diphenylbutylpiperidines (e.g. pimozide); thioxanthenes (flupentixol and zuclopenthixol); substituted benzamides (e.g. sulpiride); oxypertine; and loxapine.

Carcinogenicity. See Effects on Endocrine Function, below.

Convulsions. Treatment with antipsychotics can result in EEG abnormalities and lowered seizure threshold.[1] Seizures can be induced particularly in patients with a history of epilepsy or drug-induced seizures, abnormal EEG, previous electroconvulsive therapy, or pre-existing CNS abnormalities. The risk appears to be greatest at the start of antipsychotic therapy, or with high doses, or abrupt increases of dose, or with the use of more than one antipsychotic. The incidence of antipsychotic-induced convulsions is, however, probably less than 1%.

In general, the epileptic potential has been correlated with the propensity of the antipsychotic to cause sedation. Phenothiazines with marked sedative effects [group 1] such as chlorpromazine appear to present a higher risk than those with strong extrapyramidal effects [group 3]. Haloperidol appears to carry a relatively low risk of seizures. The following drugs have been suggested when classical antipsychotic therapy is considered necessary in