Prochlorperazine *(BAN, rINN)*

Chlormeprazine; Prochlorpemazine; Prochlorpérazine; Prochlorperazinum; Proclorperazina; Proklooriperatsiini; Proklorperazin. 2-Chloro-10-[3-(4-methylpiperazin-1-yl)propyl]phenothiazine.

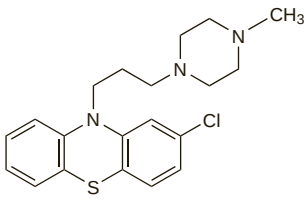
Прохлорперазин

$C_{20}H_{24}ClN_3S$ = 373.9.

CAS — 58-38-8.

ATC — N05AB04.

ATC Vet — QN05AB04.



Pharmacopoeias. In *US.*

USP 31 (Prochlorperazine). A clear, pale yellow, viscous liquid, sensitive to light. Very slightly soluble in water; freely soluble in alcohol, in chloroform, and in ether. Store in airtight containers. Protect from light.

Prochlorperazine Edisilate *(BANM, rINNM)*

Chlormeprazine Edisylate; Edisilato de proclorperazina; Prochlorpemazine Edisylate; Prochlorpérazine, Edisilate de; Prochlorperazine Edisylate; Prochlorperazine Ethanedisulphonate; Prochlorperazini Edisilas.

Прохлорперазина Эдизилат

$C_{20}H_{24}ClN_3S,C_2H_6O_6S_2$ = 564.1.

CAS — 1257-78-9.

ATC — N05AB04.

ATC Vet — QN05AB04.

Pharmacopoeias. In *US.*

USP 31 (Prochlorperazine Edisylate). A white to very light yellow odourless crystalline powder. Soluble 1 in 2 of water and 1 in 1500 of alcohol; insoluble in chloroform and in ether. Solutions in water are acid to litmus. Store in airtight containers. Protect from light.

Incompatibility. See under Prochlorperazine Mesilate, below.

Prochlorperazine Maleate *(BANM, rINNM)*

Chlormeprazine Maleate; Maleato de proclorperazina; Prochloroperazyny maleinian; Prochlorpemazine Maleate; Prochlorperazine Dihydrogen Maleate; Prochlorperazine Dimaleate; Prochlorpérazine, Maléate de; Prochlorperazini maleas; Prochlorperazinmaleinát; Prochlorperazino maleatas; Proklooriperatsiinimaleaatti; Proklorperazinmaleat; Proklórperazin-maleát.

Прохлорперазина Малеат

$C_{20}H_{24}ClN_3S,2C_4H_4O_4$ = 606.1.

CAS — 84-02-6.

ATC — N05AB04.

ATC Vet — QN05AB04.

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

Ph. Eur. 6.2 (Prochlorperazine Maleate). A white or pale yellow, crystalline powder. Very slightly soluble in water and in alcohol. A freshly prepared saturated solution in water has a pH of 3.0 to 4.0. Protect from light.

USP 31 (Prochlorperazine Maleate). A white or pale yellow, practically odourless, crystalline powder. Practically insoluble in water; soluble 1 in 1200 of alcohol; slightly soluble in warm chloroform. Its saturated solution is acid to litmus. Store in airtight containers. Protect from light.

Prochlorperazine Mesilate *(BANM, rINNM)*

Chlormeprazine Mesylate; Mesilato de proclorperazina; Prochlorpemazine Mesylate; Prochlorperazine Dimethanesulphonate; Prochlorpérazine, mésilate de; Prochlorperazine Mesylate; Prochlorperazine Methanesulphonate; Prochlorperazini mesilas; Prochlorperazini Mesylas.

Прохлорперазина Мезилат

$C_{20}H_{24}ClN_3S,2CH_3SO_3H$ = 566.2.

CAS — 5132-55-8.

ATC — N05AB04.

ATC Vet — QN05AB04.

Pharmacopoeias. In *Br.*

BP 2008 (Prochlorperazine Mesilate). A white or almost white, odourless or almost odourless powder. Very soluble in water; sparingly soluble in alcohol; slightly soluble in chloroform; practically insoluble in ether. A 2% solution in water has a pH of 2.0 to 3.0. Protect from light.

Incompatibility. Incompatibility has been reported between the edisilate or mesilate salts of prochlorperazine and several other compounds: these include aminophylline, amphotericin B, ampicillin sodium, aztreonam, some barbiturates, benzylpenicillin salts, calcium gluconate, cefalotin sodium, cefmetazole sodium, chloramphenicol sodium succinate, chlorothiazide sodium, dimenhydrinate, heparin sodium, hydrocortisone sodium succinate, midazolam hydrochloride, and some sulfonamides. Incompatibility between prochlorperazine edisilate and morphine sulfate has been attributed to phenol present in some formulations of the opioid.[1,2] Incompatibility has been reported on dilution of prochlorperazine edisilate injection with sodium chloride injection containing methyl hydroxybenzoate and propyl hydroxybenzoate as preservatives.[3] The problem did not occur with unpreserved sodium chloride or when benzyl alcohol was used as preservative. Prochlorperazine mesilate syrup has been reported to be incompatible with magnesium trisilicate mixture.[4]

1. Stevenson JG, Patriarca C. Incompatibility of morphine sulfate and prochlorperazine edisylate in syringes. *Am J Hosp Pharm* 1985: **42:** 2651.
2. Zuber DEL. Compatibility of morphine sulfate injection and prochlorperazine edisylate injection. *Am J Hosp Pharm* 1987; **44:** 67.
3. Jett S, *et al.* Prochlorperazine edisylate incompatibility. *Am J Hosp Pharm* 1983; **40:** 210.
4. Greig JR. Stemetil syrup and magnesium trisilicate. *Pharm J* 1986; **237:** 504.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p.969. Prochlorperazine may cause less sedation and fewer antimuscarinic effects but extrapyramidal effects may be more frequent.

Severe dystonic reactions have followed the use of prochlorperazine, particularly in children and adolescents. It should therefore be used with extreme care in children. In addition, in the UK, parenteral use in children is not recommended.

Local irritation has occurred after the use of buccal tablets of prochlorperazine maleate.

Effects on the cardiovascular system. Hypertension has been reported[1] in a few patients given prochlorperazine intravenously for prophylaxis of cisplatin-induced nausea and vomiting.

1. Roche H, *et al.* Hypertension and intravenous antidopaminergic drugs. *N Engl J Med* 1985; **312:** 1125–6.

Effects on the mouth. Reports of ulceration and soreness of the lip and tongue have been associated with use of prochlorperazine maleate oral tablets.[1,2] The erosive cheilitis resolved after withdrawal of prochlorperazine and recurred on rechallenge.

1. Duxbury AJ, *et al.* Erosive cheilitis related to prochlorperazine maleate. *Br Dent J* 1982; **153:** 271–2.
2. Reilly GD, Wood ML. Prochlorperazine—an unusual cause of lip ulceration. *Acta Derm Venereol (Stockh)* 1984; **64:** 270–1.

Interactions

As for Chlorpromazine, p.973.

Pharmacokinetics

◊ The pharmacokinetics of prochlorperazine were studied in 8 healthy subjects after doses of 6.25 and 12.5 mg intravenously, and 25 mg by mouth.[1] There was a marked interindividual variation in pharmacokinetics after intravenous doses but no evidence of dose-dependent pharmacokinetics; mean terminal half-lives were 6.8 hours for the higher and 6.9 hours for the lower dose. The apparent volume of distribution was very high and plasma clearance values were apparently greater than liver plasma flow, suggesting that the liver may not be the only site of metabolism. After oral doses, prochlorperazine concentrations were detectable in only 4 of the 8 subjects, due in part to a low bioavailability but also to the lack of sensitivity of the high-pressure liquid chromatographic assay used. The time to peak plasma concentration varied from 1.5 to 5 hours, and the peak concentrations varied from 1.6 to 7.6 nanograms/mL. Bioavailability was estimated to range from 0 to 16%. A low bioavailability due to high first-pass metabolism would be expected because of the high plasma clearance of prochlorperazine.

1. Taylor WB, Bateman DN. Preliminary studies of the pharmacokinetics and pharmacodynamics of prochlorperazine in healthy volunteers. *Br J Clin Pharmacol* 1987; **23:** 137–42.

Buccal route. Both single- and multiple-dose studies indicated that bioavailability of prochlorperazine maleate was greater after buccal doses than when given orally.[1,2] Doses of 3 mg twice daily by the buccal route and 5 mg three times daily by mouth produced similar steady-state plasma-prochlorperazine concentrations.[1]

1. Hessell PG, *et al.* A comparison of the availability of prochlorperazine following im buccal and oral administration. *Int J Pharmaceutics* 1989; **52:** 159–64.
2. Finn A, *et al.* Bioavailability and metabolism of prochlorperazine administered via the buccal and oral delivery route. *J Clin Pharmacol* 2005; **45:** 1383–90.

Uses and Administration

Prochlorperazine is a phenothiazine antipsychotic with general properties similar to those of chlorpromazine (p.975). It has a piperazine side-chain. Prochlorperazine and its salts are widely used in the prevention and treatment of nausea and vomiting (p.1700) including that associated with migraine or drug-induced emesis. They are also used for the short-term symptomatic relief of vertigo (p.565) as occurs in Ménière's disease (p.564) or labyrinthitis, and in the management of schizophrenia (p.955), mania (see Bipolar Disorder, p.372), and other psychoses. Prochlorperazine has been used as an adjunct in the short-term management of severe anxiety (p.952).

Prochlorperazine maleate is generally administered by the oral or buccal routes, while prochlorperazine edisilate and mesilate are given orally or parenterally. The base has been given rectally.

Depending on the country or the manufacturer, doses of prochlorperazine are expressed either as the base or the salt. Prochlorperazine edisilate 7.5 mg, prochlorperazine maleate 8.1 mg, or prochlorperazine mesilate 7.6 mg are equivalent to about 5 mg of prochlorperazine. Most doses in the UK are expressed in terms of the maleate or mesilate, while most doses in the USA are expressed in terms of the base. As a result there is a disparity in the dosage recommendations for these countries, with the doses in the USA tending to be higher.

Reduced dosage may be required in elderly patients.

For **nausea and vomiting** doses are as follows:

- in the UK, the usual *oral* dose for prevention is 5 to 10 mg of the maleate or mesilate (roughly equivalent to about 3 to 6.5 mg of the base) 2 or 3 times daily
- for the treatment of nausea and vomiting, recommended UK doses are 20 mg of the maleate or mesilate *orally* or 12.5 mg of the mesilate by deep *intramuscular* injection; further doses, preferably orally, are given if necessary. The recommended *buccal* dose of prochlorperazine maleate for this indication is 3 to 6 mg twice daily
- in the USA, the *oral* dose for the control of nausea and vomiting is the equivalent of 5 or 10 mg of the base (as edisilate or maleate) given 3 or 4 times daily; alternatively the equivalent of 10 mg of the base twice daily or 15 mg once daily of the base (both as the maleate) may be taken as modified-release capsules. The recommended *intramuscular* dosage is the equivalent of 5 to 10 mg of the base (as edisilate) given every 3 to 4 hours if necessary, up to a total of 40 mg of the base daily. The *rectal* dose is 25 mg of the base given twice daily. In the management of severe nausea and vomiting the equivalent of 2.5 to 10 mg of prochlorperazine (as the edisilate) may be given by slow *intravenous* injection or infusion at a rate not exceeding 5 mg/minute; doses should not exceed 40 mg daily

For treatment of **psychoses** the following doses have been given:

- in the UK, prochlorperazine maleate or mesilate may be given in an *oral* dose of 12.5 mg twice daily for 7 days adjusted gradually to 75 to 100 mg daily according to response; some patients may be maintained on doses of 25 to 50 mg daily. The equivalent of prochlorperazine mesilate 12.5 to 25 mg two or three times daily may be given by deep *intramuscular* injection
- in the USA, prochlorperazine is given as the maleate or edisilate in usual initial *oral* doses equivalent to 5 or 10 mg of the base 3 or 4 times daily adjusted according to response up to a maximum of 150 mg of base daily. In acute disturbances it may be given by deep *intramuscular* injection as the edisilate in doses equivalent to 10 to 20 mg of the base and repeated every 2 to 6 hours if necessary

There are similar discrepancies with **children's doses**. Owing to the risk of severe extrapyramidal reactions, prochlorperazine should be used with extreme caution in children; it is not recommended for very young children or those weighing less than 10 kg. Where use in

children is unavoidable, UK licensed product information has suggested that 250 micrograms/kg of the maleate or mesilate may be given orally 2 or 3 times daily to children aged 1 year and over for the prevention and treatment of nausea and vomiting; the intramuscular route is considered unsuitable. However, the *BNFC* suggests giving intramuscular doses, repeated up to 3 times daily if necessary, according to age as follows: 2 to 5 years, 1.25 to 2.5 mg; 5 to 12 years, 5 to 6.25 mg.

In the USA oral, rectal, and intramuscular routes have all been advocated for children aged 2 years and over. The usual oral or rectal antiemetic dose ranges up to 7.5 mg of the base or its equivalent daily in children weighing 10 to 13 kg; in children 14 to 17 kg, up to 10 mg daily; from 18 to 39 kg, up to 15 mg daily. Higher doses have been given for psychoses. The suggested intramuscular dose for children in the USA is the equivalent of about 130 micrograms/kg of base given as a single deep intramuscular injection of the edisilate.

Oral doses of 5 to 10 mg of the maleate or mesilate (or, in the USA, the equivalent of 5 mg of the base) up to 3 or 4 times daily have been used for short-term adjunctive management of **severe anxiety disorders**. A modified-release preparation may be given in doses similar to those used in nausea and vomiting.

Prochlorperazine is also used in the UK in the treatment of **vertigo** including that due to Ménière's disease. It is given *orally* in doses of 15 to 30 mg of the maleate or mesilate daily in divided doses; after several weeks the dose may be gradually reduced to 5 to 10 mg daily. The recommended *buccal* dose of prochlorperazine maleate for this indication is 3 to 6 mg twice daily.

Headache. Some phenothiazines such as prochlorperazine have been used in the control of the symptoms of severe migraine (see p.976). In comparative studies[1,2] prochlorperazine appears to have been more effective in relieving migraine headache and nausea and vomiting than metoclopramide when these drugs were given parenterally. Intravenous prochlorperazine was shown to be effective in aborting intractable migraine in children in a small uncontrolled study.[3]

1. Coppola M, *et al.* Randomized, placebo-controlled evaluation of prochlorperazine versus metoclopramide for emergency department treatment of migraine headache. *Ann Emerg Med* 1995; **26:** 541–6.
2. Jones J, *et al.* Intramuscular prochlorperazine versus metoclopramide as single-agent therapy for the treatment of acute migraine headache. *Am J Emerg Med* 1996; **14:** 262–4.
3. Kabbouche MA, *et al.* Tolerability and effectiveness of prochlorperazine for intractable migraine in children. *Pediatrics* 2001; **107:** 767. Full version: http://pediatrics.aappublications.org/cgi/content/full/107/4/e62 (accessed 28/04/04)

Preparations

BP 2008: Prochlorperazine Buccal Tablets; Prochlorperazine Injection; Prochlorperazine Oral Solution; Prochlorperazine Tablets;
USP 31: Prochlorperazine Edisylate Injection; Prochlorperazine Maleate Tablets; Prochlorperazine Oral Solution; Prochlorperazine Suppositories.

Proprietary Preparations (details are given in Part 3)

Austral.: Stemetil; Stemzine; ***Canad.:*** Apo-Prochlorazine; Nu-Prochlor; Stemetil; ***Denm.:*** Stemetil; ***Fin.:*** Stemetil; ***Hong Kong:*** Dhaperazine; Seratil; Stemetil; ***India:*** Bukatel†; Emidoxyn; Stemetil; Vometil; ***Irl.:*** Buccastem; Stemetil; ***Ital.:*** Stemetil; ***Malaysia:*** Dhaperazine; Nautisol; Prochlor; Stemetil†; ***Neth.:*** Stemetil; ***Norw.:*** Stemetil; ***NZ:*** Antinaus; Buccastem; Stemetil; ***Pol.:*** Chloropernazinum; ***S.Afr.:*** Mitil; Scripto-Metic; Stemetil; ***Singapore:*** Dhaperazine; Prochlor; Stemetil; ***Swed.:*** Stemetil; ***Thai.:*** Proclozine; Stemetil; ***UK:*** Buccastem; Prozieret; Stemetil; ***USA:*** Compazine; Compro.

Multi-ingredient: ***Ital.:*** Difmetre.

Promazine *(BAN, rINN)*

A-145; NSC-31447; Promatsiini; Promazin; Promazina; Promazinum; Propazinum; 3276-RP; RP-3276; WY-1094. *NN*-Dimethyl-3-phenothiazin-10-ylpropylamine.

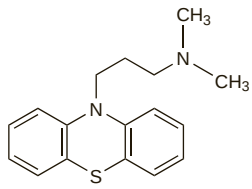
Промазин

$C_{17}H_{20}N_2S$ = 284.4.

CAS — 58-40-2.

ATC — N05AA03.

ATC Vet — QN05AA03.



NOTE. The code A-145 has also been used for *N*-ethylcarbaminomethyl-*L*-isoleucine, a compound investigated as an antineoplastic

Promazine Embonate *(BANM, rINNM)*

Embonato de promazina; Promazine, Embonate de; Promazine Pamoate; Promazini Embonas.

Промазина Эмбонат

$(C_{17}H_{20}N_2S)_2,C_{23}H_{16}O_6$ = 957.2.

ATC — N05AA03.

ATC Vet — QN05AA03.

Promazine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de promazina; Promatsiinihydrokloridi; Promazine, chlorhydrate de; Promazin-hidroklorid; Promazin-hydrochlorid; Promazinhydroklorid; Promazini hydrochloridum; Promazino hidrochloridas; Promazyny chlorowodorek.

Промазина Гидрохлорид

$C_{17}H_{20}N_2S$,HCl = 320.9.

CAS — 53-60-1.

ATC — N05AA03.

ATC Vet — QN05AA03.

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

Ph. Eur. 6.2 (Promazine Hydrochloride). A white or almost white, slightly hygroscopic, crystalline powder. Very soluble in water, in alcohol, and in dichloromethane. A freshly prepared 5% solution in water has a pH of 4.2 to 5.2. Protect from light.

USP 31 (Promazine Hydrochloride). A white or slightly yellow, practically odourless, crystalline powder. It oxidises upon prolonged exposure to air and acquires a pink or blue colour. Soluble 1 in 3 of water; freely soluble in chloroform. pH of a 1 in 20 solution is between 4.2 and 5.2. Store in airtight containers. Protect from light.

Incompatibility. Incompatibility has been reported between promazine hydrochloride and several other compounds: these include aminophylline, some barbiturates, benzylpenicillin potassium, chlortetracycline, chlorothiazide sodium, dimenhydrinate, heparin sodium, hydrocortisone sodium succinate, phenytoin sodium, prednisolone sodium phosphate, and sodium bicarbonate.

Sorption. A study[1] of drug loss from intravenous delivery systems reported an 11% loss of promazine hydrochloride from solution when infused for 7 hours via a plastic infusion set, and a 59% loss after infusion for one hour from a glass syringe through silastic tubing. 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.

Stability. A study of the stability of promazine diluted to a 0.1% infusion in sodium chloride 0.9% or glucose 5% found that solutions in glucose 5% remained stable for up to 6 days at 4°, and at room temperature, provided they were stored in the dark.[1] However, with sodium chloride 0.9% as the diluent, deterioration of promazine was observed 24 hours after preparation, even when stored in the dark, and after 8 hours when exposed to light. Temperature had no effect on degradation rate.

1. Tebbett IR, *et al.* Stability of promazine as an intravenous infusion. *Pharm J* 1986; **237:** 172–4.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p.969.

Pregnancy. An increased incidence of neonatal jaundice coincided with the increased use of promazine.[1] A decrease in the incidence of jaundice was noted 3 months after the total withdrawal of the drug from the hospital although restriction of its use during labour had no impact.

1. John E. Promazine and neonatal hyperbilirubinaemia. *Med J Aust* 1975; **2:** 342–4.

Interactions

As for Chlorpromazine, p.973.

Pharmacokinetics

The pharmacokinetics of promazine appear to be generally similar to those of chlorpromazine (p.975).

Uses and Administration

Promazine is a phenothiazine with general properties similar to those of chlorpromazine (p.975). It has relatively weak antipsychotic activity and is not generally used for the management of psychoses. It is mainly used for the short-term management of agitated or disturbed behaviour (p.954). It has also been given for the alleviation of nausea and vomiting (p.1700). Promazine is given as the hydrochloride by mouth, intramuscularly, or by slow intravenous injection. Promazine has also been given by mouth as the embonate.

For the treatment of **agitated behaviour**, promazine is given in doses equivalent to 100 to 200 mg of the hydrochloride 4 times daily by mouth or 50 mg by intramuscular injection repeated if necessary after 6 to 8 hours. It has also been given by slow intravenous injection in concentrations not exceeding 25 mg/mL, for severely agitated hospitalised patients.

An oral dose of 25 to 50 mg every 4 to 6 hours has been given for the control of **nausea and vomiting**; it has also been given by intramuscular injection for this indication.

Promazine should be given in reduced dosage to elderly or debilitated patients; 25 mg orally of the hydrochloride initially, increasing, if necessary, to 50 mg four times daily has been suggested for the control of agitation and restlessness; for intramuscular injection, a dose of 25 mg may be sufficient.

Hiccup. Promazine hydrochloride has been used in some countries for the treatment of intractable hiccup. A protocol for the management of intractable hiccups may be found under Chlorpromazine, p.976.

Preparations

BP 2008: Promazine Injection; Promazine Tablets;
USP 31: Promazine Hydrochloride Injection; Promazine Hydrochloride Oral Solution; Promazine Hydrochloride Syrup; Promazine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Belg.: Prazine†; ***Denm.:*** Sparine†; ***Fin.:*** Sparine†; ***Ger.:*** Protactyl†; Sinophenin†; ***Gr.:*** Sinophenin; Sparine†; ***Ital.:*** Talofen; ***S.Afr.:*** Sparine; ***Switz.:*** Prazine; ***USA:*** Prozine.

Propionylpromazine

Dipropimazine; Propionilpromazina; Propiopromazine.

CAS — 3568-24-9.

Profile

Propionylpromazine is a phenothiazine antipsychotic that has been used for sedation and premedication in veterinary medicine.

Prothipendyl Hydrochloride *(BANM, rINNM)*

D-206; Hidrocloruro de protipendilo; Phrenotropin; Prothipendyl, Chlorhydrate de; Prothipendyli Hydrochloridum. *NN*-Dimethyl-3-(pyrido[3,2-*b*][1,4]benzothiazin-10-yl)propylamine hydrochloride monohydrate.

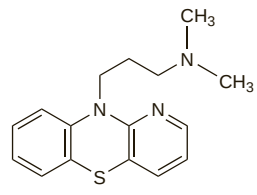
Протипендила Гидрохлорид

$C_{16}H_{19}N_3S$,HCl,H_2O = 339.9.

CAS — 303-69-5 (prothipendyl); 1225-65-6 (anhydrous prothipendyl hydrochloride).

ATC — N05AX07.

ATC Vet — QN05AX07.



(prothipendyl)

Profile

Prothipendyl is an azaphenothiazine with general properties similar to those of chlorpromazine (p.969). It is given as the hydrochloride in oral doses of 40 to 80 mg two to four times daily for the treatment of psychoses and agitation, and as an adjunct to analgesics in the treatment of severe pain. Prothipendyl hydrochloride may also be given by injection.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Dominal; ***Belg.:*** Dominal; ***Ger.:*** Dominal.