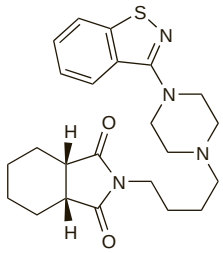
Perospirone Hydrochloride *(rINNM)*

Hidrocloruro de perospirona; Pérospirone, Chlorhydrate de; Perospironi Hydrochloridum; SM-9018. *cis*-*N*-{4-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]butyl}-1,2-cyclohexanedicarboximide hydrochloride.

Пероспирона Гидрохлорид

$C_{23}H_{30}N_4O_2S,HCl$ = 463.0.

CAS — 150915-41-6 (perospirone); 129273-38-7 (perospirone hydrochloride).



(perospirone)

Profile

Perospirone is an antipsychotic used in the treatment of schizophrenia. Although it has been described as an atypical antipsychotic, the incidence of extrapyramidal effects may be rather higher than is usually seen with atypical drugs such as clozapine (p.981). Perospirone hydrochloride is given in usual oral doses of 12 to 48 mg daily in 3 divided doses.

◊ References.

1. Onrust SV, McClellan K. Perospirone. *CNS Drugs.* 2001; **15:** 329–37.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Lullan.

Perphenazine *(BAN, rINN)*

Perfenatsiini; Perfenazin; Perfenazina; Perfenazinas; Perfenazyna; Perphénazine; Perphenazinum. 2-{4-[3-(2-Chlorophenothiazin-10-yl)propyl]piperazin-1-yl}ethanol.

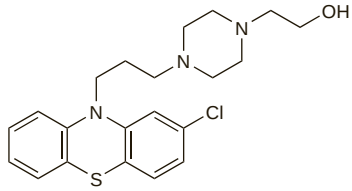
Перфеназин

$C_{21}H_{26}ClN_3OS$ = 404.0.

CAS — 58-39-9.

ATC — N05AB03.

ATC Vet — QN05AB03.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*. *Jpn* also includes the maleate.

Ph. Eur. 6.2 (Perphenazine). A white or yellowish-white crystalline powder. Practically insoluble in water; soluble in alcohol; freely soluble in dichloromethane; dissolves in dilute solutions of hydrochloric acid. Protect from light.

USP 31 (Perphenazine). A white to creamy-white odourless powder. M.p. 94° to 100°. Practically insoluble in water; soluble 1 in 7 of alcohol and 1 in 13 of acetone; freely soluble in chloroform. Store in airtight containers. Protect from light.

Incompatibility. Perphenazine has been reported to be incompatible with cefoperazone sodium[1] and with midazolam hydrochloride (see p.1007).

1. Gasca M, *et al.* Visual compatibility of perphenazine with various antimicrobials during simulated Y-site injection. *Am J Hosp Pharm* 1987; **44:** 574–5.

Perphenazine Decanoate *(BANM, rINNM)*

Decanoato de perfenazina; Perphénazine, Décanoate de; Perphenazini Decanoas.

Перфеназина Деканоат

$C_{31}H_{44}ClN_3O_2S$ = 558.2.

ATC — N05AB03.

ATC Vet — QN05AB03.

Perphenazine Enantate *(BANM, rINNM)*

Enantato de perfenazina; Perphénazine, Enantate de; Perphenazine Enanthate; Perphenazine Heptanoate; Perphenazini Enantas.

Перфеназина Энантат

$C_{28}H_{38}ClN_3O_2S$ = 516.1.

CAS — 17528-28-8.

ATC — N05AB03.

ATC Vet — QN05AB03.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p.969. Perphenazine has been associated with a lower frequency of sedation, but a higher incidence of extrapyramidal effects.

Breast feeding. The American Academy of Pediatrics[1] considers that, although the effect of perphenazine on breast-fed infants is unknown, its use by mothers during breast feeding may be of concern since antipsychotics do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

The distribution of perphenazine into breast milk was studied[2] in a mother who was receiving oral perphenazine 24 mg daily, later reduced to 16 mg daily. Breast feeding was started after it was estimated that a breast-fed infant would ingest about 0.1% of a maternal dose. Treatment with perphenazine lasted for 3.5 months and during this period the child thrived normally and no drug-induced symptoms were seen.

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. Olesen OV, *et al.* Perphenazine in breast milk and serum. *Am J Psychiatry* 1990; **147:** 1378–9.

Interactions

As for Chlorpromazine, p.973.

Pharmacokinetics

Perphenazine is well absorbed after oral doses and undergoes some first-pass metabolism, resulting in a relative bioavailability of about 60 to 80%. Peak plasma concentrations are achieved between 1 to 3 hours after ingestion. It is widely distributed and crosses the placenta. Perphenazine is extensively metabolised; up to 70% is excreted in the urine mainly as metabolites, with about 5% being excreted in the faeces. The plasma elimination half-life of perphenazine is between 9 and 12 hours. Perphenazine decanoate and perphenazine enantate are slowly absorbed from the site of intramuscular injection. They gradually release perphenazine into the body and are therefore suitable for use as depot injections.

◊ Perphenazine 5 or 6 mg given intravenously had a plasma half-life from 8.4 to 12.3 hours in a study of 4 schizophrenic patients and 4 healthy subjects.[1] Plasma-perphenazine concentrations varied considerably 3 to 5 hours after dosing; this was followed by an exponential elimination phase. Plasma concentrations were undetectable after a 6-mg oral dose in 4 healthy subjects and only low plasma concentrations of its sulfoxide metabolite could be detected; this was attributed to a marked first-pass effect. Systemic availability was also variable and poor in 4 schizophrenic patients given perphenazine 12 mg three times daily. However, it was considered that oral therapy should be given at 8-hour intervals. Intramuscular injection of perphenazine enantate 50 or 100 mg every 2 weeks gave plasma-perphenazine concentrations similar to those after continuous oral dosage, but high initial absorption in the first 2 to 3 days was associated with serious CNS adverse effects.

1. Hansen CE, *et al.* Clinical pharmacokinetic studies of perphenazine. *Br J Clin Pharmacol* 1976; **3:** 915–23.

Metabolism. In a study in 12 healthy subjects there was a clear difference in the disposition of a single oral dose of perphenazine between poor and extensive hydroxylators of debrisoquine.[1]

1. Dahl-Puustinen M-L, *et al.* Disposition of perphenazine is related to polymorphic debrisoquin hydroxylation in human beings. *Clin Pharmacol Ther* 1989; **46:** 78–81.

Uses and Administration

Perphenazine is a phenothiazine with general properties similar to those of chlorpromazine (p.975). It has a piperazine side-chain. It is used in the treatment of various psychoses including schizophrenia (p.955) and mania (see Bipolar Disorder, p.372) as well as disturbed behaviour (p.954) and in the short-term, adjunctive management of severe anxiety (p.952). Perphenazine is also used for the management of postoperative or chemotherapy-induced nausea and vomiting (p.1700) and for the treatment of intractable hiccup (p.976).

Perphenazine is usually given orally and sometimes by intramuscular or intravenous injection as the base. Long-acting decanoate or enantate esters of perphenazine, available in some countries, are given by intramuscular injection.

The usual initial oral dose for the treatment of **schizophrenia, mania, and other psychoses** is 4 mg three times daily. The dose is adjusted according to response up to a usual maximum of 24 mg daily, although up to 64 mg daily has occasionally been used in hospitalised patients. Similar doses have been used for the management of **severe agitated or violent behaviour** or in **severe anxiety**. Perphenazine has sometimes been used in preparations with tricyclic antidepressants such as amitriptyline in the treatment of anxiety with depression.

For the **control of nausea and vomiting** the usual oral dose is 4 mg three times daily but up to 8 mg three times daily may be required.

Perphenazine may be given by deep *intramuscular* injection for control of acute psychotic symptoms or for severe nausea and vomiting. An initial dose of 5 or 10 mg is followed, if necessary, by 5 mg every 6 hours to a maximum of 15 to 30 mg daily.

Perphenazine, diluted to a concentration of 500 micrograms/mL in sodium chloride 0.9%, is occasionally given by *intravenous* injection in divided doses, not more than 1 mg being given every 1 to 2 minutes; the maximum intravenous dose is 5 mg. The intravenous route is usually reserved for the control of severe vomiting or intractable hiccup. Perphenazine has also been given by slow infusion.

The long-acting decanoate or enantate esters of perphenazine are given by deep intramuscular injection in doses ranging from about 50 to 300 mg of ester given at intervals of 2 to 4 weeks.

Perphenazine and its esters should be given in reduced doses to the elderly but it should be noted that they are not indicated for the management of agitation and restlessness in these patients.

◊ References.

1. Hartung B, *et al.* Perphenazine for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 14/04/05).

Preparations

BP 2008: Perphenazine Tablets;
USP 31: Perphenazine and Amitriptyline Hydrochloride Tablets; Perphenazine Injection; Perphenazine Oral Solution; Perphenazine Syrup; Perphenazine Tablets.

Proprietary Preparations (details are given in Part 3)
Austria: Decentan; ***Belg.:*** Trilafon†; ***Canad.:*** Trilafon; ***Denm.:*** Trilafon; ***Fin.:*** Peratsin; ***Fr.:*** Trilifan; ***Ger.:*** Decentan; ***Indon.:*** Trilafon; ***Israel:*** Perphenan; ***Ital.:*** Trilafon; ***Mex.:*** Leptopsique; Trilafon†; ***Neth.:*** Trilafon; ***Norw.:*** Trilafon; ***Philipp.:*** Trilafon; ***Pol.:*** Trilafon; ***S.Afr.:*** Trilafon†; ***Spain:*** Decentan; ***Swed.:*** Trilafon; ***Switz.:*** Trilafon; ***Thai.:*** Conazine; Pernamed; Pernazine; Perzine†; Porazine; ***UK:*** Fentazin; ***USA:*** Trilafon†.

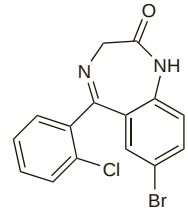
Multi-ingredient: ***Arg.:*** Karile; Mutabon D†; ***Canad.:*** PMS-Levazine; Triavil†; ***Chile:*** Mutabon D†; ***Fin.:*** Pertriptyl; ***Gr.:*** Minitran; ***Indon.:*** Mutabon-D; Mutabon-M; ***Ital.:*** Mutabon; ***Mex.:*** Adepsique; ***Port.:*** Mutabon; ***S.Afr.:*** Etrafon†; ***Spain:*** Mutabase; ***Thai.:*** Anxipress-D†; Neuragon; Polybon; ***UK:*** Triptafen; ***USA:*** Etrafon; Triavil†.

Phenazepam

Fenazepam. 7-Bromo-5-(2-chlorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one.

$C_{15}H_{10}BrClN_2O$ = 349.6.

CAS — 51753-57-2.



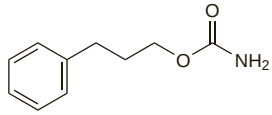
Profile
Phenazepam is a benzodiazepine with general properties similar to those of diazepam (p.986). It is used in the short-term treatment of anxiety disorders and as an anticonvulsant.

Phenprobamate *(BAN, rINN)*

Fenprobamaatti; Fenprobamat; Fenprobamato; MH-532; Phenprobamatum; Proformiphen. 3-Phenylpropyl carbamate.

Фенпробамат

$C_{10}H_{13}NO_2$ = 179.2.
CAS — 673-31-4.
ATC — M03BA01.
ATC Vet — QM03BA01.



Profile
Phenprobamate is a carbamate with general properties similar to those of meprobamate (p.1006). It has been used for its anxiolytic and muscle relaxant actions.

Preparations

Proprietary Preparations (details are given in Part 3)
Turk.: Gamaflex; Gamakuil.

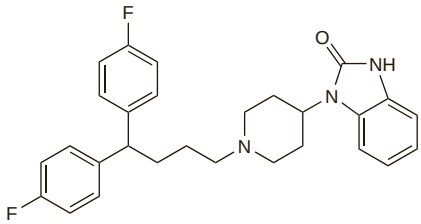
Multi-ingredient: ***Turk.:*** Kuiflex; Kuilil.

Pimozide *(BAN, USAN, rINN)*

McN-JR-6238; Pimotsidi; Pimozid; Pimozida; Pimozidas; Pimozidum; Pimozyd; R-6238. 1-{1-[4,4-Bis(4-fluorophenyl)butyl]-4-piperidyl}benzimidazolin-2-one; 1-{1-[3-(4,4′-Difluorobenzhydryl)propyl]-4-piperidyl}benzimidazolin-2-one.

Пимозид

$C_{28}H_{29}F_2N_3O$ = 461.5.
CAS — 2062-78-4.
ATC — N05AG02.
ATC Vet — QN05AG02.



Pharmacopoeias. In *Eur.* (see p.vii) and *US.*
Ph. Eur. 6.2 (Pimozide). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol; soluble in dichloromethane; sparingly soluble in methyl alcohol. Protect from light.
USP 31 (Pimozide). A white crystalline powder. Insoluble in water; soluble 1 in 1000 of alcohol, of ether, and of methyl alcohol, 1 in 100 of acetone, 1 in 10 of chloroform, and 1 in more than 1000 of 0.1N hydrochloric acid. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p.969.

Extrapyramidal effects may be more common than with chlorpromazine but pimozide may be less likely to cause sedation, hypotension, or antimuscarinic effects.

Ventricular arrhythmias and other ECG abnormalities, such as prolongation of the QT interval and T-wave changes, have been associated with the use of pimozide; an ECG should therefore be performed before, and repeated periodically during, treatment. If repolarisation changes appear or arrhythmias develop, the need for continuing treatment should be reviewed; the dose of pimozide should be reduced or, if the QT interval exceeds 500 milliseconds, therapy should be withdrawn. Pimozide is contra-indicated in patients with pre-existing prolongation of the QT interval, or a family history of congenital QT prolongation, and in patients with a history of cardiac arrhythmias. Electrolyte disturbances such as hypokalaemia or hypomagnesaemia in patients receiving pimozide may lead to cardiotoxicity.

Effects on the cardiovascular system. The UK CSM has received reports of ventricular arrhythmias and other ECG abnormalities such as prolongation of the QT interval and T-wave changes associated with the use of pimozide.[1,2] In August 1990 they had received 13 reports of sudden unexpected death since 1971; many of these patients had no evidence of pre-existing cardiac disease, and 7 were under 30 years of age. Five of the 13 were also taking other antipsychotics. Most cases were associated with doses greater than 20 mg daily and many had had the dose increased rapidly, possibly resulting in substantial tissue accumulation. By February 1995 the CSM had received a total of 40 reports (16 fatal) of serious cardiac reactions most of which involved arrhythmias.

See also under Chlorpromazine, p.970.

1. CSM. Cardiotoxic effects of pimozide. *Current Problems 29* 1990. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024447&RevisionSelectionMethod=LatestReleased (accessed 07/08/08)
2. CSM/MCA. Cardiac arrhythmias with pimozide (Orap). *Current Problems* 1995; **21:** 2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015618&RevisionSelectionMethod=LatestReleased (accessed 16/05/06)

Interactions

As for Chlorpromazine, p.973. The risk of arrhythmias with pimozide may be increased by other drugs that prolong the QT interval including some antiarrhythmics, other antipsychotics (including depot preparations), tricyclic antidepressants, the antihistamines terfenadine and astemizole, antimalarials, and cisapride; use together should be avoided. Use with drugs that induce electrolyte disturbances, such as diuretics, should also be avoided.

The use of pimozide with drugs that inhibit the cytochrome P450 isoenzyme CYP3A4 is contra-indicated; the resultant decrease in the metabolism of pimozide may lead to increased plasma concentrations and hence greater risk of cardiac arrhythmias. CYP3A4 inhibitors include the macrolide antibacterials such as clarithromycin, erythromycin, and troleandomycin; the azole antifungals including itraconazole and ketoconazole; the HIV-protease inhibitors; the NNRTIs; nefazodone, and zileuton. The metabolism of pimozide may also be inhibited by grapefruit juice and use together should be avoided.

Pimozide is also metabolised by CYP2D6, albeit to a lesser extent, and *in vitro* data indicate that the CYP2D6 inhibitor quinidine may reduce the metabolism of pimozide; UK licensed product information contra-indicates the use of such inhibitors with pimozide. The isoenzyme CYP1A2 may also be involved in the metabolism of pimozide and consequently there is a theoretical possibility of interactions with CYP1A2 inhibitors.

Pimozide should also not be used with SSRIs such as citalopram, escitalopram, paroxetine, and sertraline.

Antibacterials. Sudden deaths have occurred in patients given pimozide and *clarithromycin*, see p.973.

Pharmacokinetics

More than half of an oral dose of pimozide is reported to be absorbed. It undergoes significant first-pass metabolism. Peak plasma concentrations have been reported after 4 to 12 hours and there is a considerable interindividual variation in the concentrations achieved. Pimozide is metabolised in the liver mainly by *N*-dealkylation and excreted in the urine and faeces in the form of metabolites and unchanged drug. Metabolism is mediated mainly by the cytochrome P450 isoenzyme CYP3A4 and to a lesser extent by CYP2D6; CYP1A2 may also be involved. Pimozide has a mean elimination half-life of about 55 hours, although half-lives of up to 150 hours have been noted in some patients.

Uses and Administration

Pimozide is a diphenylbutylpiperidine antipsychotic and is structurally similar to the butyrophenones. It is a long-acting antipsychotic with general properties similar to those of the phenothiazine, chlorpromazine (p.975), although it also has some calcium-blocking activity. Pimozide is given orally in the management of psychoses including schizophrenia, paranoid states, and monosymptomatic hypochondria (p.954) and in Tourette's syndrome. An ECG should be performed in all patients before starting treatment with pimozide (see Adverse Effects, Treatment, and Precautions, above).

In **schizophrenia**, treatment is usually begun with a dose of 2 mg daily (the *BNFC* suggests 1 mg in those aged 12 to 18 years), adjusted thereafter according to response in increments of 2 to 4 mg at intervals of not less than 1 week. A maximum daily dose of 20 mg should not be exceeded. It is usually given as a single daily dose.

In **monosymptomatic hypochondria** and **paranoid psychoses**, the initial dose is 4 mg daily adjusted as above to a maximum daily dose of 16 mg.

Pimozide treatment should start at half the usual initial dosage in elderly patients.

In the USA, pimozide is used for the treatment of **Tourette's syndrome** in an initial dose of 1 to 2 mg daily in divided doses; children may be given 50 micrograms/kg daily initially. Dosage may be increased gradually to a maximum of 10 mg daily or 200 micrograms/kg daily; data are limited in children under 12 years of age. Although not licensed in the UK for the treatment of Tourette's syndrome, the *BNFC* suggests that children aged from 2 to 12 years may be given 1 to 4 mg daily and those aged from 12 to 18 years, 2 to 10 mg daily.

Chorea. Antipsychotics such as pimozide have some action against choreiform movements (p.953) as well as being of use to control the behavioural disturbances of Huntington's chorea.

References.

1. Shannon KM, Fenichel GM. Pimozide treatment of Sydenham's chorea. *Neurology* 1990; **40:** 186.

Dystonia. Antipsychotics such as phenothiazines, haloperidol, or pimozide are sometimes useful in the treatment of idiopathic dystonia (p.809) in patients who have failed to respond to other drugs.[1] In very severe dystonia combination therapy may be required. Pimozide in gradually increasing doses up to 12 mg daily with tetrabenazine and trihexyphenidyl is sometimes effective. However, antipsychotics often act non-specifically and there is the risk of adding drug-induced extrapyramidal disorders to the dystonia being treated (see Extrapyramidal Disorders under Adverse Effects of Chlorpromazine, p.971).

1. Marsden CD, Quinn NP. The dystonias. *BMJ* 1990; **300:** 139–44.

Schizophrenia. A systematic review[1] concluded that pimozide appears to be of similar efficacy to other classical antipsychotics in the treatment of schizophrenia (p.955). There was no evidence that it was particularly useful for those with delusional disorders or with mainly negative symptoms.

1. Rathbone J, McMonagle T. Pimozide for schizophrenia or related psychoses. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 20/03/08).

Taste disorders. For reference to the use of pimozide in the treatment of taste disorders, see Chlorpromazine, p.977.

Tourette's syndrome. Tourette's syndrome (see Tics, p.954) is a disorder characterised by motor and vocal tics and behavioural disturbances. Many patients with Tourette's syndrome do not require medication but when treatment is needed dopamine antagonists such as the antipsychotics haloperidol or pimozide[1,2] have been most commonly used. They often decrease the frequency and severity of tics and may improve any accompanying behavioural disturbances. However, superiority of either drug in terms of efficacy or adverse effects has not been clearly demonstrated. Because of the potential for acute and long-term adverse effects it is usually recommended that doses are titrated to as low as possible; the aim of treatment is not necessarily to control symptoms completely. Medication can often be stopped after a few years.

1. Shapiro E, *et al.* Controlled study of haloperidol, pimozide, and placebo for the treatment of Gilles de la Tourette's syndrome. *Arch Gen Psychiatry* 1989; **46:** 722–30.
2. Sallee FR, *et al.* Relative efficacy of haloperidol and pimozide in children and adolescents with Tourette's disorder. *Am J Psychiatry* 1997; **154:** 1057–62.