

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.

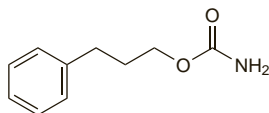
Фенпробамат

$C_{10}H_{13}NO_2 = 179.2$.

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; Gamakul.

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.

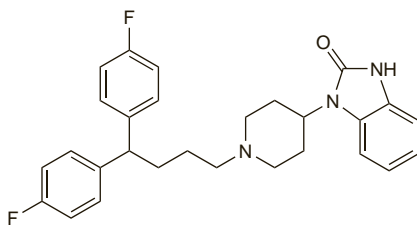
ПИМОЗИД

$C_{28}H_{29}F_2N_3O = 461.5$.

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 review¹ 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.