Pramipexole Hydrochloride

(BANM, rINNM)

Hidrocloruro de pramipexol; PNU-98528-E; Pramipexole, Chlorhydrate de; Pramipexole, dichlorhydrate de; Pramipexole Dihydrochloride *(USAN)*; Pramipexoli dihydrochloridum; Pramipexoli Hydrochloridum; SND-919-CL-2Y (pramipexole hydrochloride); SUD-919Y (pramipexole). (*S*)-2-Amino-4,5,6,7-tetrahydro-6-(propylamino)benzothiazole dihydrochloride monohydrate.

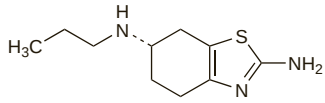
Прамипексола Гидрохлорид

$C_{10}H_{17}N_3S,2HCl, H_2O$ = 302.3.

CAS — 104632-26-0 (pramipexole); 104632-25-9 (anhydrous pramipexole hydrochloride); 191217-81-9 (pramipexole hydrochloride monohydrate).

ATC — N04BC05.

ATC Vet — QN04BC05.



(pramipexole)

Adverse Effects and Precautions

As for Bromocriptine, p.798.

Pramipexole should be used with caution in patients with renal impairment and reduced doses are recommended.

Ophthalmological monitoring is recommended at regular intervals or if vision abnormalities occur.

Incidence of adverse effects. References.

1. Etminan M, *et al.* Comparison of the risk of adverse events with pramipexole and ropinirole in patients with Parkinson's disease: a meta-analysis. *Drug Safety* 2003; **26:** 439–44.

Effects on mental function. Pramipexole has been associated with attacks of sudden onset of sleep, sometimes without any prior feeling of drowsiness, that can occur at any time during treatment. Licensed product information states that the incidence of daytime **somnolence** is increased at daily doses of pramipexole hydrochloride higher than 1.5 mg. A retrospective analysis[1] of data to evaluate the incidence and nature of somnolence in patients receiving pramipexole in clinical studies showed that for patients with moderate or severe somnolence, the onset of worst-reported somnolence occurred at a mean daily dose of around 4 mg (range: 0.75 to 4.5 mg).

For further reports of daytime somnolence occurring in patients receiving dopamine agonists including pramipexole, see under Adverse Effects of Levodopa, p.805.

For reference to **pathological gambling** reported in patients with Parkinson's disease receiving dopamine agonists, including pramipexole, see under Levodopa, p.805.

1. Hauser RA, *et al.* Pramipexole-induced somnolence and episodes of daytime sleep. *Mov Disord* 2000; **15:** 658–63.

Interactions

As for Bromocriptine, p.800. Cimetidine is reported to reduce the renal clearance of pramipexole.

Caution is advised when other sedating drugs or alcohol are used with pramipexole because of possible additive effects and the risk of precipitating sudden onset of sleep (see above).

◊ References.

1. Wright CE, *et al.* Influence of probenecid and cimetidine on pramipexole pharmacokinetics. *Clin Pharmacol Ther* 1996; **59:** 183.

Pharmacokinetics

Pramipexole is readily absorbed from the gastrointestinal tract and peak plasma concentrations have been reached within about 2 hours in fasting patients and in about 3 hours when given with food. Oral bioavailability is reported to be about 90%. Pramipexole is widely distributed throughout the body and plasma-protein binding is less than 20%. Metabolism is minimal and more than 90% of a dose is excreted via renal tubular secretion unchanged into the urine. Elimination half-lives of 8 to 12 hours have been reported. On the basis of studies in *rats*, it is thought to be distributed into breast milk.

◊ References.

1. Wright CE, *et al.* Steady-state pharmacokinetic properties of pramipexole in healthy volunteers. *J Clin Pharmacol* 1997; **37:** 520–5.

Uses and Administration

Pramipexole is a non-ergot dopamine agonist with actions similar to those of bromocriptine (p.800). It is used similarly in the management of Parkinson's disease, either alone or as an adjunct to levodopa therapy to reduce 'end-of-dose' or 'on-off' fluctuations in response. Pramipexole is also used for the treatment of moderate to severe restless legs syndrome. It is given orally as the hydrochloride; doses have been described in terms of the hydrochloride (as below) or of the base. In terms of equivalency:

- pramipexole hydrochloride 125 micrograms is equivalent to about 88 micrograms of pramipexole
- pramipexole hydrochloride 250 micrograms is equivalent to about 180 micrograms of pramipexole
- pramipexole hydrochloride 500 micrograms is equivalent to about 350 micrograms of pramipexole
- pramipexole hydrochloride 1 mg is equivalent to about 700 micrograms of pramipexole

In the treatment of **Parkinson's disease**, the dose of pramipexole should be increased gradually and the dose of levodopa gradually reduced during the dose-titration and maintenance phases until an optimum response is achieved. The initial dose of pramipexole *hydrochloride* is 125 micrograms three times daily increased to 250 micrograms three times daily in the second week and then to 500 micrograms three times daily in the third week according to response. Thereafter the daily dose may be increased if necessary by 750 micrograms at weekly intervals to a maximum of 4.5 mg daily. The dosage should be reduced in patients with renal impairment (see below).

If it is necessary to stop pramipexole therapy, it should be withdrawn gradually. UK licensed product information suggests tapering off the dose of pramipexole hydrochloride at a rate of 750 micrograms daily until a daily dose of 750 micrograms has been reached; thereafter, the dose should be reduced by 375 micrograms daily. US licensed product information suggests that withdrawal should be gradual over a period of 1 week.

Pramipexole is also given as a single daily dose, 2 to 3 hours before bedtime, in the treatment of **restless legs syndrome**. The initial dose of pramipexole *hydrochloride* is 125 micrograms daily. This may be increased if necessary after 4 to 7 days to 250 micrograms daily. Subsequent doses may be increased if necessary by 250 micrograms every 4 to 7 days to a maximum of 750 micrograms daily. Response to therapy should be evaluated after 3 months; if treatment is interrupted for more than a few days, it should be restarted at 125 micrograms daily, and then increased, if required, as described above. For this indication, pramipexole may be withdrawn without gradual tapering of the dose.

Administration in renal impairment. The elimination of pramipexole is dependent on renal function and the dosage of pramipexole hydrochloride should therefore be reduced in patients with renal impairment.

In the treatment of *Parkinson's disease*, the following dosage schedule has been suggested in UK licensed product information for initial therapy adjusted according to the patient's creatinine clearance (CC):

- CC 20 to 50 mL/minute: 125 micrograms given twice daily
- CC less than 20 mL/minute: 125 micrograms once daily

Similar reductions are suggested in US licensed information for patients with a CC of 35 to 59 mL/minute and 15 to 34 mL/minute, respectively.

If renal function declines during maintenance therapy it is recommended that the daily dose of pramipexole should be reduced by the same percentage as the decline in CC.

Lower doses are used in the treatment of *restless legs syndrome* and UK licensed information considers dosage reductions unnecessary in patients with CC of more than 20 mL/minute. US licensed information recommends that the interval between titration steps is increased to 14 days in those patients with CC of 20 to 60 mL/minute.

Parkinsonism. Pramipexole is a dopamine agonist used in the treatment of Parkinson's disease (p.791) as an adjunct to levodopa therapy to reduce 'off' periods with levodopa and ameliorate other fluctuations of mobility in the later stages of the disease. It is also used as monotherapy early in the course of the disease in an attempt to delay therapy with levodopa.

References.

1. Parkinson Study Group. Safety and efficacy of pramipexole in early Parkinson disease: a randomized dose-ranging study. *JAMA* 1997; **278:** 125–30.
2. Lieberman A, *et al.* Clinical evaluation of pramipexole in advanced Parkinson's disease: results of a double-blind, placebo-controlled, parallel-group study. *Neurology* 1997; **49:** 162–8.
3. Shannon KM, *et al.* Efficacy of pramipexole, a novel dopamine agonist, as monotherapy in mild to moderate Parkinson's disease. *Neurology* 1997; **49:** 724–8.
4. Guttman M. International Pramipexole-Bromocriptine Study Group. Double-blind comparison of pramipexole and bromocriptine treatment with placebo in advanced Parkinson's disease. *Neurology* 1997; **49:** 1060–5.
5. Parkinson Study Group. Pramipexole vs levodopa as initial treatment for Parkinson disease: a randomized controlled trial. *JAMA* 2000; **284:** 1931–8.
6. Clarke CE, *et al.* Pramipexole for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2000 (accessed 16/02/06).
7. Clarke CE, *et al.* Pramipexole versus bromocriptine for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2000 (accessed 16/02/06).
8. Parkinson Study Group. Pramipexole vs levodopa as initial treatment for Parkinson disease: a 4-year randomized controlled trial. *Arch Neurol* 2004; **61:** 1044–53. Correction. *ibid.* 2005; **62:** 430.
9. Moller JC, *et al.* Long-term efficacy and safety of pramipexole in advanced Parkinson's disease: results from a European multicenter trial. *Mov Disord* 2005; **20:** 602–10.

Restless legs syndrome. The aetiology of restless legs syndrome (RLS—see Sleep-associated Movement Disorders, p.958) is obscure and treatment has largely been empirical, although dopaminergic therapy has emerged as a common first-line choice. Low-dose pramipexole has produced some benefit in a number of studies[1-7] and is licensed for the treatment of moderate to severe RLS in some countries.

1. Lin S-C, *et al.* Effect of pramipexole in treatment of resistant restless legs syndrome. *Mayo Clin Proc* 1998; **73:** 497–500.
2. Montplaisir J, *et al.* Restless legs syndrome improved by pramipexole: a double-blind randomized trial. *Neurology* 1999; **52:** 938–43.
3. Montplaisir J, *et al.* Pramipexole in the treatment of restless legs syndrome: a follow-up study. *Eur J Neurol* 2000; **7** (suppl 1): 27–31.
4. Saletu M, *et al.* Acute placebo-controlled sleep laboratory studies and clinical follow-up with pramipexole in restless legs syndrome. *Eur Arch Psychiatry Clin Neurosci* 2002; **252:** 185–94.
5. Silber MH, *et al.* Pramipexole in the management of restless legs syndrome: an extended study. *Sleep* 2003; **26:** 819–21.
6. Stiasny-Kolster K, Oertel WH. Low-dose pramipexole in the management of restless legs syndrome: an open label trial. *Neuropsychobiology* 2004; **50:** 65–70.
7. Winkelman JW, *et al.* Efficacy and safety of pramipexole in restless legs syndrome. *Neurology* 2006; **67:** 1034–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Maxtenk; Mirapex†; Nixol; Parfeno; Parxium; Portiv; Sifrol; ***Austral.:*** Sifrol; ***Austria:*** Sifrol; ***Belg.:*** Mirapexin; ***Braz.:*** Mirapex; Sifrol; ***Canad.:*** Mirapex; ***Chile:*** Sifrol; ***Cz.:*** Mirapexin; Sifrol; ***Denm.:*** Mirapexin; Sifrol; ***Fin.:*** Sifrol; ***Fr.:*** Sifrol; ***Ger.:*** Sifrol; ***Gr.:*** Mirapexin; ***Hung.:*** Mirapexin; ***Indon.:*** Sifrol; ***Irl.:*** Mirapexin; ***Ital.:*** Mirapexin; ***Jpn:*** BI-Sifrol; ***Malaysia:*** Sifrol; ***Mex.:*** Sifrol; ***Neth.:*** Daquiran†; Sifrol; ***Norw.:*** Sifrol; ***NZ:*** Sifrol; ***Philipp.:*** Sifrol; ***Pol.:*** Mirapexin; ***Port.:*** Mirapexin; Sifrol; ***Rus.:*** Mirapex (Мирапекс); ***S.Afr.:*** Pexola; ***Singapore:*** Sifrol; ***Spain:*** Mirapexin; ***Swed.:*** Sifrol; ***Switz.:*** Sifrol; ***Thai.:*** Sifrol; ***Turk.:*** Pexola; ***UK:*** Mirapexin; ***USA:*** Mirapex; ***Venez.:*** Sifrol/Mirapex.

Procyclidine Hydrochloride

(BANM, rINNM)

Hidrocloruro de prociclidina; Procyclidine, Chlorhydrate de; Procyclidini Hydrochloridum. 1-Cyclohexyl-1-phenyl-3-(pyrrolidin-1-yl)propan-1-ol hydrochloride.

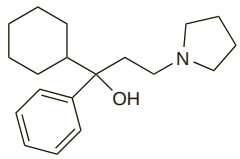
Проциклидина Гидрохлорид

$C_{19}H_{29}NO,HCl$ = 323.9.

CAS — 77-37-2 (procyclidine); 1508-76-5 (procyclidine hydrochloride).

ATC — N04AA04.

ATC Vet — QN04AA04.



(procyclidine)

Pharmacopoeias. In *Br.* and *US*.
BP 2008 (Procyclidine Hydrochloride). A white, odourless or almost odourless, crystalline powder. Sparingly soluble in water; soluble in alcohol; practically insoluble in acetone and in ether. A 1% solution in water has a pH of 4.5 to 6.5.
USP 31 (Procyclidine Hydrochloride). A white crystalline powder, having a moderate characteristic odour. Soluble 1 in 35 of water, 1 in 9 of alcohol, 1 in 6 of chloroform, and 1 in 11 000 of ether; insoluble in acetone. pH of a 1% solution in water is between 5.0 and 6.5. Store in a dry place in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p.1219. Psychotic episodes may be precipitated in patients with mental disorders when procyclidine is used for the treatment of drug-induced extrapyramidal syndrome.

Abuse. Like other antimuscarinics (see also under Trihexyphenidyl Hydrochloride, p.820) procyclidine has been abused for its euphoriant effects.[1,2]

1. McGucken RB, *et al*. Teenage procyclidine abuse. *Lancet* 1985; **i:** 1514.
2. Dooris B, Reid C. Feigning dystonia to feed an unusual drug addiction. *J Accid Emerg Med* 2000; **17:** 311.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p.1220).

Paroxetine increases plasma-procyclidine concentrations and it is recommended that the dose of procyclidine should be reduced if antimuscarinic effects are seen in patients receiving both drugs.

Pharmacokinetics

Procyclidine hydrochloride is absorbed from the gastrointestinal tract and bioavailability has been reported to be 75% after oral doses; it disappears rapidly from the tissues. Procyclidine given intravenously acts within 5 to 20 minutes and has a duration of effect of up to 4 hours. The mean plasma elimination half-life after oral or intravenous doses is about 12 hours. About one-fifth of an oral dose is metabolised in the liver, mainly by the cytochrome P450 isoenzymes, followed by conjugation with glucuronic acid. A small amount of unchanged drug is excreted in the urine.

◊ References.

1. Whiteman PD, *et al*. Pharmacokinetics and pharmacodynamics of procyclidine in man. *Eur J Clin Pharmacol* 1985; **28:** 73–8.

Uses and Administration

Procyclidine hydrochloride is a tertiary amine antimuscarinic with actions and uses similar to those of trihexyphenidyl (p.820). It is used for the symptomatic treatment of parkinsonism (p.791), including the alleviation of the extrapyramidal syndrome induced by drugs such as phenothiazines, but, like other antimuscarinics, is of no value against tardive dyskinesias. It has been used in the treatment of dystonias (but see under Uses and Administration of Levodopa, p.809).

In **parkinsonism**, the initial oral dose of 2.5 mg three times daily may be increased gradually by 2.5 to 5 mg every 2 or 3 days (or by 2.5 mg daily if used for drug-induced extrapyramidal syndrome) until the optimum maintenance dose, usually 10 to 30 mg daily in 3 (or occasionally 4) divided doses, is reached; daily doses of up to 60 mg have occasionally been required. As a rule, postencephalitic patients tolerate and require the larger doses; elderly and arteriosclerotic patients may require smaller doses.

In emergency, 5 to 10 mg may be given by intravenous injection; higher doses have sometimes been used. The intramuscular route has also been employed: 5 to 10 mg may be given as a single injection, repeated if necessary after 20 minutes to a maximum of 20 mg daily. Parenteral doses are usually effective within 5 to 10 minutes but may need 30 minutes to produce relief.

Although not licensed in the UK for management of **dystonias in children**, the *BNFC* suggests oral doses of 1.25 mg 3 times daily in those aged 7 to 12 years, and 2.5 mg 3 times daily in those aged 12 to 18 years. In an emergency, a single dose may be given by intramuscular or intravenous injection to children as follows: aged under 2 years, 0.5 to 2 mg; 2 to 10 years, 2 to 5 mg; 10 to 18 years, 5 to 10 mg or occasionally more.

Preparations

BP 2008: Procyclidine Injection; Procyclidine Tablets;
USP 31: Procyclidine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Austria: Kemadrin; ***Belg.:*** Kemadrin; ***Canad.:*** Kemadrin†; Procyclid†; ***Cz.:*** Kemadrin; ***Denm.:*** Kemadrin; ***Ger.:*** Osnervan; ***Hung.:*** Kemadrin; ***India:*** Kemadrin; ***Irl.:*** Kemadrin; ***Israel:*** Kemadrin; ***Ital.:*** Kemadrin†; ***Malaysia:*** Kemadrin†; ***NZ:*** Kemadrin; ***Spain:*** Kemadren; ***Switz.:*** Kemadrin; ***UK:*** Arpicolin; Kemadrin; Muscinil†; ***USA:*** Kemadrin.

Profenamine Hydrochloride *(BANM, rINNM)*

Cloridrato de Profenamina; Ethopropazine Hydrochloride; Hidrocloruro de profenamina; Isothazine Hydrochloride; Profénamine, Chlorhydrate de; Profenamini Hydrochloridum; Prophenamini Chloridum. 10-(2-Diethylaminopropyl)phenothiazine hydrochloride.

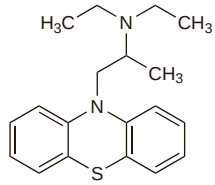
Профенамина Гидрохлорид

$C_{19}H_{24}N_2S,HCl$ = 348.9.

CAS — 522-00-9 (profenamine); 1094-08-2 (profenamine hydrochloride).

ATC — N04AA05.

ATC Vet — QN04AA05.



(profenamine)

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p.1219.

Profenamine may also cause muscle cramps, paraesthesia, and a sense of heaviness in the limbs, epigastric discomfort, and nausea.

Profenamine is a phenothiazine derivative; adverse effects associated with phenothiazines may occur, especially with high doses (see under Chlorpromazine, p.969).

Breast feeding. Profenamine is distributed into the milk of lactating mothers.[1]

1. Rowan JJ. Excretion of drugs in milk. *Pharm J* 1976; **217:** 184–7.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p.1220).

Uses and Administration

Profenamine hydrochloride is a phenothiazine derivative with antimuscarinic, adrenergic-blocking, antihistaminic, local anaesthetic, and ganglion-blocking properties. It has been used in the symptomatic treatment of parkinsonism (p.791), including the alleviation of the extrapyramidal syndrome induced by drugs such as other phenothiazines, but, like other antimuscarinics, is of no value against tardive dyskinesias. It has been used in a usual initial oral dose of 50 mg three times daily, gradually increased to 500 mg or more daily in divided doses, according to response.

Preparations

Proprietary Preparations (details are given in Part 3)
Canad.: Parsitan.

Rasagiline Mesilate *(rINNM)*

Mesilato de rasagilina; Rasagiline, Mésilate de; Rasagiline Mesylate *(USAN)*; Rasagilini Mesilas; TVP-1012. (*R*)-*N*-2-Propynyl-1-indanamine methanesulfonate.

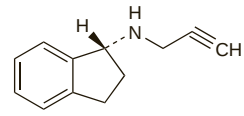
Разагилина Мезилат

$C_{12}H_{13}N,CH_4O_3S$ = 267.3.

CAS — 136236-51-6 (rasagiline); 161735-79-1 (rasagiline mesilate).

ATC — N04BD02.

ATC Vet — QN04BD02.



(rasagiline)

Adverse Effects and Precautions

Common adverse effects reported with rasagiline monotherapy include headache, flu-like syndrome, malaise, neck pain, angina pectoris, dyspepsia, anorexia, leucopenia, arthralgia, arthritis, depression, vertigo, rhinitis, conjunctivitis, skin rashes, melanoma, and urinary urgency. Cerebrovascular accidents and myocardial infarction have been reported rarely. Other adverse effects include orthostatic hypotension and hallucinations.

Rasagiline should not be used in patients with severe hepatic impairment; use in moderate impairment should also be avoided. It should be used with caution in patients with mild hepatic impairment and therapy should be stopped in those who progress to moderate impairment.

Interactions

As for Selegiline Hydrochloride, p.817. Unlike the non-selective MAOIs, such as phenelzine, rasagiline can be used safely without dietary tyramine restrictions, although these have been recommended in some countries.

Rasagiline should not be given with other MAOIs because of the risk of non-selective MAO inhibition that may lead to hypertensive reactions.

It is metabolised by the cytochrome P450 isoenzyme CYP1A2 and potent inhibitors of this enzyme such as ciprofloxacin may increase the plasma levels of rasagiline. UK licensed product information for rasagiline advises caution when such drugs are used with rasagiline whereas US licensed product information recommends that the dose of rasagiline be reduced to 0.5 mg daily when given with CYP1A2 inhibitors. Tobacco smoking induces hepatic metabolic enzymes and may decrease the plasma levels of rasagiline.

Entacapone has been reported to increase the clearance of oral rasagiline by 28% when used together.

Pharmacokinetics

Rasagiline is rapidly absorbed from the gastrointestinal tract, with peak plasma levels occurring in about 30 minutes to an hour. Bioavailability is reported to be about 36%. Rasagiline is about 60 to 70% bound to plasma proteins.

It is extensively metabolised in the liver by *N*-dealkylation and hydroxylation, via the cytochrome P450 isoenzyme CYP1A2, and conjugation. 1-Aminoindan is a major metabolite and is stated to be active although it is not a monoamine oxidase B inhibitor. Metabolites are excreted mainly in the urine and partly in the faeces; less than 1% of a dose is excreted as unchanged drug in the urine. The terminal half-life is 0.6 to 2 hours.

Uses and Administration

Rasagiline is an irreversible selective inhibitor of monoamine oxidase type B, an enzyme involved in the metabolic degradation of dopamine in the brain. It enhances the effects of levodopa and is used in the treatment of Parkinson's disease (p.791), either alone or as an adjunct to levodopa therapy to reduce 'end-of-dose' fluctuations in response. Rasagiline is given orally as the mesilate and doses are expressed in terms of the base; rasagiline mesilate 1.56 mg is equivalent to about 1 mg of rasagiline. The usual dose is the equivalent of rasagiline 1 mg once daily. In the USA, an initial daily dose of 0.5 mg is recommended for adjunctive therapy.

The dose of rasagiline may need to be reduced when given with drugs that inhibit the cytochrome P450 isoenzyme CYP1A2 (see Interactions, above for details) and in patients with hepatic impairment (see below).

◊ References.

1. Parkinson Study Group. A controlled trial of rasagiline in early Parkinson disease: the TEMPO Study. *Arch Neurol* 2002; **59:** 1937–43.
2. Stern MB, *et al*. Double-blind, randomized, controlled trial of rasagiline as monotherapy in early Parkinson's disease patients. *Mov Disord* 2004; **19:** 916–23.
3. Thebault JJ, *et al*. Tolerability, safety, pharmacodynamics, and pharmacokinetics of rasagiline: a potent, selective, and irreversible monoamine oxidase type B inhibitor. *Pharmacotherapy* 2004; **24:** 1295–1305.
4. Parkinson Study Group. A controlled, randomized, delayed-start study of rasagiline in early Parkinson disease. *Arch Neurol* 2004; **61:** 561–6.