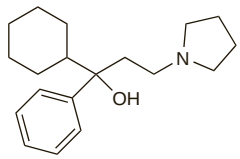


(procyclidine)

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.

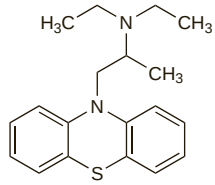
Профенамина Гидрохлорид

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

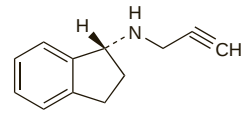
Разагилина Мезилат

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

5. Parkinson Study Group. A randomized placebo-controlled trial of rasagiline in levodopa-treated patients with Parkinson disease and motor fluctuations: the PRESTO study. *Arch Neurol* 2005; **62:** 241–8.
6. Rascol O, *et al.* Rasagiline as an adjunct to levodopa in patients with Parkinson's disease and motor fluctuations (LARGO, Lasting effect in Adjunct therapy with Rasagiline Given Once daily, study): a randomised, double-blind, parallel-group trial. *Lancet* 2005; **365:** 947–54.
7. Rascol O. Rasagiline in the pharmacotherapy of Parkinson's disease: a review. *Expert Opin Pharmacother* 2005; **6:** 2061–75.
8. Chen JJ, *et al.* Clinical pharmacology of rasagiline: a novel, second-generation propargylamine for the treatment of Parkinson disease. *J Clin Pharmacol* 2005; **45:** 878–94.
9. Siderowf A, Stern M. Clinical trials with rasagiline: evidence for short-term and long-term effects. *Neurology* 2006; **66** (suppl 4): S80–S88.
10. Oldfield V, *et al.* Rasagiline: a review of its use in the management of Parkinson's disease. *Drugs* 2007; **67:** 1725–47.

Administration in hepatic impairment. UK licensed product information for rasagiline advises caution when used in patients with mild hepatic impairment whereas US licensed information recommends that the dose be reduced to 500 micrograms daily. Rasagiline should not be used in those with moderate or severe impairment.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Elbrus; ***Belg.:*** Azilect; ***Cz.:*** Azilect; ***Denm.:*** Azilect; ***Fin.:*** Azilect; ***Fr.:*** Azilect; ***Ger.:*** Azilect; ***Gr.:*** Azilect; ***Irl.:*** Azilect; ***Israel:*** Azilect; ***Neth.:*** Azilect; ***Norw.:*** Azilect; ***Pol.:*** Azilect; ***Port.:*** Azilect; ***Spain:*** Azilect; ***UK:*** Azilect; ***USA:*** Azilect.

Ropinirole Hydrochloride

(BANM, USAN, pINNM)

Hidrocloruro de ropinirol; Ropinirole, Chlorhydrate de; Ropiniroli Hydrochloridum; SKF-101468 (ropinirole); SKF-0101468-A (ropinirole hydrochloride). 4-[2-(Dipropylamino)ethyl]-2-indolinone hydrochloride.

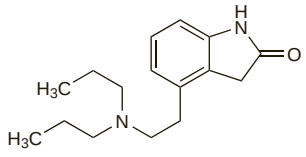
Ропинирола Гидрохлорид

$C_{16}H_{24}N_2O,HCl$ = 296.8.

CAS — 91374-21-9 (ropinirole); 91374-20-8 (ropinirole hydrochloride).

ATC — N04BC04.

ATC Vet — QN04BC04.



(ropinirole)

Adverse Effects and Precautions

As for Bromocriptine, p.798. Licensed product information states that the pharmacokinetics of ropinirole have not been studied in patients with hepatic or severe renal impairment and therefore it should be used with caution, if at all, in such patients. No pharmacokinetic changes were noted in those with mild to moderate renal impairment.

In the treatment of restless legs syndrome, earlier onset of symptoms in the afternoon or evening (augmentation) and recurrence of symptoms in the early morning hours (rebound) have been reported with ropinirole.

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

Interactions

Since it is a dopamine agonist, ropinirole may share some of the pharmacological interactions of bromocriptine, p.800. In addition, high doses of oestrogens can increase plasma concentrations of ropinirole and dosage adjustments may be necessary if oestrogen therapy is started or withdrawn during treatment with ropinirole. Ropinirole is metabolised by the cytochrome P450 isoenzyme CYP1A2 and there is therefore the potential for interactions between ropinirole and other drugs that are metabolised similarly or more particularly with inducers or inhibitors of this enzyme. Dosage adjustments may be necessary if therapy with such drugs is started or withdrawn during treatment with ropinirole.

Pharmacokinetics

Ropinirole is rapidly absorbed from the gastrointestinal tract and mean peak plasma concentrations have been achieved 1.5 hours after oral doses; the rate of absorption, but not the extent, may be reduced if taken with food. Bioavailability is reported to be about 50%. It is widely distributed throughout the body and plasma protein binding is low (10 to 40%).

Ropinirole is extensively metabolised in the liver, primarily by the cytochrome P450 isoenzyme CYP1A2, and excreted in the urine as inactive metabolites; less than 10% of an oral dose is excreted as unchanged drug. A mean elimination half-life of about 6 hours has been reported for ropinirole. It is thought to be distributed into breast milk on the basis of studies in *rats*.

◊ References.

1. Brefel C, *et al.* Effect of food on the pharmacokinetics of ropinirole in parkinsonian patients. *Br J Clin Pharmacol* 1998; **45:** 412–15.
2. Hubble J, *et al.* Linear pharmacokinetic behavior of ropinirole during multiple dosing in patients with Parkinson's disease. *J Clin Pharmacol* 2000; **40:** 641–6.
3. Kaye CM, Nicholls B. Clinical pharmacokinetics of ropinirole. *Clin Pharmacokinet* 2000; **39:** 243–54.

Uses and Administration

Ropinirole is a non-ergot dopamine D_2-agonist with similar actions to those of bromocriptine (p.800), but in contrast to bromocriptine it also has agonist properties at D_3 receptors. It is used similarly in the management of Parkinson's disease, either alone or as an adjunct to reduce 'on-off' fluctuations in levodopa response. Ropinirole is also used for the treatment of moderate to severe idiopathic restless legs syndrome. It is given by mouth as the hydrochloride; doses are expressed in terms of the base. Ropinirole hydrochloride 1.14 mg is equivalent to about 1 mg of ropinirole.

In the treatment of **Parkinson's disease**, ropinirole should be introduced gradually and during this period patients already receiving levodopa can have their levodopa dosage decreased gradually until an optimal response is achieved; the concurrent dose of levodopa may be reduced by about 20 to 30%. The daily dosage of ropinirole should be given in three divided doses, preferably with food. The initial daily dose of ropinirole is 750 micrograms increased at weekly intervals in steps of 750 micrograms for the first 4 weeks. After week 4, the weekly increments may be made in steps of 1.5 mg up to a dose of 9 mg daily according to response; subsequent weekly increments may be made in steps of up to 3 mg. The daily dosage should not exceed 24 mg. Optimal response is usually achieved within the range of 3 to 9 mg daily; higher doses may be required if used with levodopa. If it is necessary to stop ropinirole therapy, it should be withdrawn gradually by reducing the number of daily doses over the period of 1 week. Once adequate symptomatic control has been established, ropinirole may be given as once-daily modified-release tablets.

Ropinirole is also given as a single daily dose, 1 to 3 hours before bedtime, in the treatment of **restless legs syndrome**. The initial dose of ropinirole is 250 micrograms daily for 2 days; if tolerated, the dose is then increased to 500 micrograms daily for the rest of the first week. Subsequent increases may be made in weekly steps of 500 micrograms until a dose of 3 mg daily is reached; if necessary, the dose may then be increased after 1 further week to a maximum of 4 mg daily.

In the UK, it has been recommended that treatment should be re-assessed 3 months after starting therapy. For this indication, ropinirole may be withdrawn without gradual tapering of the dose.

If treatment with ropinirole is interrupted for more than a few days it should be restarted at the low initial dose and increased gradually as required.

◊ Reviews.

1. Tulloch IF. Pharmacologic profile of ropinirole: a nonergoline dopamine agonist. *Neurology* 1997; **49** (suppl 1): S58–S62.

Parkinsonism. Dopamine agonists such as ropinirole may be used to begin treatment of parkinsonism (p.791) in an attempt to delay therapy with levodopa, particularly in younger patients. They also have an adjunctive use when levodopa is no longer effective alone or cannot be tolerated, and may be useful in reducing 'off' periods with levodopa and in ameliorating other fluctuations of mobility in the later stage of the disease.

References.

1. Rascol O, *et al.* A placebo-controlled study of ropinirole a new D agonist, in the treatment of motor fluctuations of -DOPA-treated parkinsonian patients. *Adv Neurol* 1996; **69:** 531–4.
2. Adler CH, *et al.* The Ropinirole Study Group. Ropinirole for the treatment of early Parkinson's disease. *Neurology* 1997; **49:** 393–9.
3. Rascol O, *et al.* Ropinirole in the treatment of early Parkinson's disease: a 6-month interim report of a 5-year levodopa-controlled study. *Mov Disord* 1998; **13:** 39–45.
4. Korczyn AD, *et al.* A 3-year randomized trial of ropinirole and bromocriptine in early Parkinson's disease. *Neurology* 1999; **53:** 364–70.
5. Matheson AJ, Spencer CM. Ropinirole: a review of its use in the management of Parkinson's disease. *Drugs* 2000; **60:** 115–37.
6. Clarke CE, Deane KHO. Ropinirole for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2001 (accessed 16/02/06).
7. Clarke CE, Deane KHO. Ropinirole versus bromocriptine for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews: Issue 1. Chichester: John Wiley; 2001 (accessed 16/02/06).
8. Whone AL, *et al.* Slower progression of Parkinson's disease with ropinirole versus levodopa: the REAL-PET study. *Ann Neurol* 2003; **54:** 93–101.
9. Pahwa R, *et al.* Ropinirole 24-hour prolonged release: randomized, controlled study in advanced Parkinson disease. *Neurology* 2007; **68:** 1108–15.

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. Ropinirole is licensed for the treatment of moderate to severe RLS in some countries.

References.

1. Trenkwalder C, *et al.* Ropinirole in the treatment of restless legs syndrome: results from the TREAT RLS 1 study, a 12 week, randomised, placebo controlled study in 10 European countries. *J Neurol Neurosurg Psychiatry* 2004; **75:** 92–7.
2. Cheer SM, *et al.* Ropinirole: for the treatment of restless legs syndrome. *CNS Drugs* 2004; **18:** 747–54.
3. Walters AS, *et al.* Ropinirole is effective in the treatment of restless legs syndrome—TREAT RLS 2: a 12-week, double-blind, randomized, parallel-group, placebo-controlled study. *Mov Disord* 2004; **19:** 1414–23.
4. Bogan RK, *et al.* TREAT RLS US Study Group. Ropinirole in the treatment of patients with restless legs syndrome: a US-based randomized, double-blind, placebo-controlled clinical trial. *Mayo Clin Proc* 2006; **81:** 17–27.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Requip; ***Austral.:*** Repreve; ***Austria:*** Requip; ***Belg.:*** Requip; ***Canad.:*** Requip; ***Chile:*** Requip; ***Cz.:*** Adartrel; Requip; ***Denm.:*** Requip; ***Fin.:*** Requip; ***Fr.:*** Adartrel; Requip; ***Ger.:*** Requip; ***Gr.:*** Adartrel; Requip; ***Hong Kong:*** Requip; ***Hung.:*** Requip; ***Irl.:*** Requip; ***Israel:*** Requip; ***Ital.:*** Requip; ***Malaysia:*** Requip; ***Neth.:*** Requip; ***Norw.:*** Requip; ***NZ:*** Requip; ***Pol.:*** Requip; ***Port.:*** Requip; Zyatrol; ***S.Afr.:*** Requip; ***Singapore:*** Requip; ***Spain:*** Requip; ***Swed.:*** Requip; ***Switz.:*** Adartrel; Requip; ***Turk.:*** Requip; ***UK:*** Adartrel; Requip; ***USA:*** Requip.

Rotigotine *(USAN, rINN)*

N-0923; Rotigotina; Rotigotinum; SPM-962. (–)-(*S*)-5,6,7,8-Tetrahydro-6-{propyl[2-(2-thienyl)ethyl]amino}-1-naphthol.

Ротиготин

$C_{19}H_{25}NOS$ = 315.5.

CAS — 99755-59-6 (rotigotine); 125572-93-2 (rotigotine hydrochloride).

ATC — N04BC09.

ATC Vet — QN04BC09.