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.

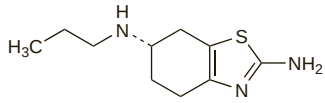
Прамипексола Гидрохлорид

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