## Lisuride Maleate *(BANM, rINNM)*

Lisurid Maleat; Lisuride, Maléate de; Lisuridi Hydrogenomaleas; Lisuridi Maleas; Lisuridivetymaleaatti; Lisuridvätemaleat; Lysuride Maleate; Maleato de lisurida; Methylergol Carbamide Maleate. 3-(9,10-Didehydro-6-methylergolin-8α-yl)-1,1-diethylurea hydrogen maleate; 8-Decarboxamido-8-(3,3-diethylureido)-D-lysergamide maleate.

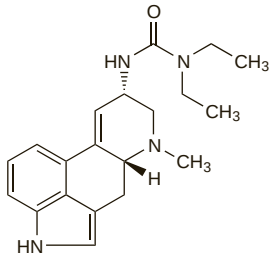
Лизурида Малеат

$C_{20}H_{26}N_4O,C_4H_4O_4$ = 454.5.

*CAS — 18016-80-3 (lisuride); 19875-60-6 (lisuride maleate).*

*ATC — G02CB02; N02CA07.*

*ATC Vet — QG02CB02; QN02CA07.*



*(lisuride)*

### Adverse Effects and Precautions

As for Bromocriptine, p.798. Infusion of lisuride in parkinsonian patients has been associated with severe psychiatric adverse effects.

**Effects on mental function.** For reports of daytime somnolence occurring in patients receiving dopamine agonists including lisuride, see under Adverse Effects of Levodopa, p.805.

**Fibrosis.** For reports of fibrotic reactions occurring in patients with Parkinson's disease receiving ergot derivative dopamine agonists including lisuride, see under Adverse Effects of Bromocriptine, p.799.

**Porphyria.** Lisuride maleate is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

### Interactions

As for Bromocriptine, p.800.

### Pharmacokinetics

◊ Plasma concentrations varied widely after a single oral dose of lisuride maleate 300 micrograms in 11 patients with Parkinson's disease.[1] Absorption was rapid and the mean plasma elimination half-life was 2.2 hours. Only a mean of 0.05% of the dose was excreted unchanged in the urine in 24 hours. The mean oral bioavailability of lisuride maleate has been reported[2] to be 10% after a 100-microgram dose and 22% after a 300-microgram dose.

A single dose of lisuride 25 micrograms given by intravenous, intramuscular, or subcutaneous injection reduced plasma-prolactin concentrations by up to 60% in 11 of 12 healthy subjects, the effect lasting for about 10 hours.[3] Plasma-lisuride concentrations after intravenous injection fell in 2 phases with half-lives of 14 minutes and 1.5 hours, respectively. Peak plasma concentrations after subcutaneous and intramuscular injection were obtained after 12 and 15 minutes, respectively.


1. Burns RS, *et al*. Disposition of oral lisuride in Parkinson's disease. *Clin Pharmacol Ther* 1984; **35:** 548–56.
2. Hümpel M, *et al*. Radioimmunoassay of plasma lisuride in man following intravenous and oral administration of lisuride hydrogen maleate; effect on plasma prolactin level. *Eur J Clin Pharmacol* 1981; **20:** 47–51.
3. Krause W, *et al*. The pharmacokinetics and pharmacodynamics of lisuride in healthy volunteers after intravenous, intramuscular, and subcutaneous injection. *Eur J Clin Pharmacol* 1991; **40:** 399–403.


### Uses and Administration

Lisuride maleate, an ergot derivative, is a dopamine $D_2$-agonist with actions and uses similar to those of bromocriptine (p.798). It is also reported to have serotonergic activity. It is used similarly in the management of Parkinson's disease and has been used in disorders associated with hyperprolactinaemia. It is also used to suppress puerperal lactation for medical reasons; it is not recommended for the routine suppression of physiological lactation or for the treatment of postpartum breast pain and engorgement that can be adequately relieved with simple analgesics and breast support. Lisuride has been used in some countries for the treatment of acromegaly, and for the prophylaxis of migraine.

In the management of **Parkinson's disease** lisuride maleate has been given alone or added to treatment in patients having 'on-off' fluctuations in control with levodopa. It is normally given orally; doses should be taken with food. Initially 200 micrograms is taken at bedtime and additional doses of 200 micrograms may be added, at intervals of one week, first at midday and then in the morning. Further increases are made, until an optimum response is obtained, by adding 200 micrograms each week using the same sequence of increases, starting with the bedtime dose; dosage should not normally exceed 5 mg daily in divided doses.

**Acromegaly.** Dopaminergics can produce a paradoxical reduction in growth hormone secretion and may be used in the treatment of acromegaly as adjunctive therapy to surgery, radiotherapy, or somatostatin analogues to reduce circulating growth hormone levels, although they are less effective than somatostatin analogues (p.1798). While bromocriptine has been the main dopamine agonist used, lisuride has been used in some countries, typically in a dose of 100 micrograms three times daily.

**Hyperprolactinaemia and prolactinomas.** Dopamine agonists have been widely used for the treatment of hyperprolactinaemia secondary to a prolactinoma (p.2079). Lisuride has been used as an alternative to bromocriptine. There is a report of plasma-prolactin concentrations being reduced to normal in 4 female patients with macroprolactinomas given lisuride 400 to 800 micrograms daily for 2 years.[1] Subsequent dosage reduction in 3 was followed by a rise in prolactin values. In the fourth patient prolactin remained in the normal range when the dose was progressively reduced from 400 to 50 micrograms daily, although complete withdrawal was followed by an increase in prolactin concentration within 3 months.

Vaginal dosage of lisuride has been studied in an attempt to avoid adverse effects associated with oral therapy. In a study[2] involving 40 women with hyperprolactinaemia a 200-microgram standard oral tablet placed in the vagina at night produced a similar reduction in prolactin concentrations to that obtained with 400 micrograms taken orally and was better tolerated.


1. Liuzzi A, *et al*. Low doses of dopamine agonists in the long-term treatment of macroprolactinomas. *N Engl J Med* 1985; **313:** 656–9.
2. Tasdemir M, *et al*. Vaginal lisuride for hyperprolactinaemia. *Lancet* 1995; **346:** 1362.


**Lactation inhibition.** Lisuride is used in some countries for the prevention of puerperal lactation (p.2003). However, the routine use of dopaminergics is not recommended for the suppression of physiological lactation.

References.


1. Venturini PL, *et al*. Effects of lisuride and bromocriptine on inhibition of lactation and on serum prolactin levels: comparative double-blind study. *Eur J Obstet Gynecol Reprod Biol* 1981; **11:** 395–400.


**Mastalgia.** In a small placebo-controlled study,[1] lisuride 200 micrograms daily was effective in the treatment of cyclical mastalgia. However, since mastalgia (p.2092) can improve spontaneously, treatment should rarely be considered unless pain has been present for about 6 months.


1. Kaleli S, *et al*. Symptomatic treatment of premenstrual mastalgia in premenopausal women with lisuride maleate: a double-blind placebo-controlled randomized study. *Fertil Steril* 2001; **75:** 718–23.


**Migraine.** Although lisuride has been used in some countries for the prophylaxis of migraine (p.616) it is not usually considered to be the drug of choice or even one of the main alternatives.

**Parkinsonism.** While some neurologists use dopamine agonists such as lisuride early in the treatment of parkinsonism (p.791) in an attempt to delay therapy with levodopa, others reserve them for adjunctive use when levodopa is no longer effective alone or cannot be tolerated. They are sometimes useful in reducing 'off' periods with levodopa and in ameliorating other fluctuations in mobility in the later stages of the disease.

References.


1. Rinne UK. Lisuride, a dopamine agonist in the treatment of early Parkinson's disease. *Neurology* 1989; **39:** 336–9.
2. Clarke CE, Speller JM. Lisuride for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 1999 (accessed 16/02/06).
3. Clarke CE, Speller JM. Lisuride versus bromocriptine for levodopa-induced complications in Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 1999 (accessed 16/02/06).
4. Allain H, *et al.* Five-year follow-up of early lisuride and levodopa combination therapy versus levodopa monotherapy in de novo Parkinson's disease. *Eur Neurol* 2000; **44:** 22–30.


***ADMINISTRATION.*** Lisuride has been of benefit when given by continuous intravenous or subcutaneous infusion in patients having fluctuations in mobility with levodopa therapy[1-4] but severe psychiatric effects have been associated with the use of these routes.[3] Transdermal lisuride is also being investigated for the treatment of Parkinson's disease and restless legs syndrome.[5,6]


1. Obeso JA, *et al.* Intravenous lisuride corrects oscillations of motor performance in Parkinson's disease. *Ann Neurol* 1986; **19:** 31–5.
2. Obeso JA, *et al*. Lisuride infusion pump: a device for the treatment of motor fluctuations in Parkinson's disease. *Lancet* 1986; **i:** 467–70.
3. Critchley P, *et al.* Psychosis and the lisuride pump. *Lancet* 1986; **i:** 349.
4. Stocchi F, *et al.* Prospective randomized trial of lisuride infusion versus oral levodopa in patients with Parkinson's disease. *Brain* 2002; **125:** 2058–66.
5. Woitalla D, *et al.* Transdermal lisuride delivery in the treatment of Parkinson's disease. *J Neural Transm Suppl* 2004; **68:** 89–95.
6. Benes H. Transdermal lisuride: short-term efficacy and tolerability study in patients with severe restless legs syndrome. *Sleep Med* 2006; **7:** 31–5.


### Preparations

**Proprietary Preparations** (details are given in Part 3)

***Arg.:*** Dopagon†; ***Austria:*** Dopergin; Prolacam†; ***Fr.:*** Arolac; Dopergine; ***Ger.:*** Cuvalit†; Dopergin; ***Gr.:*** Dipergon; ***Ital.:*** Dopergin; ***Mex.:*** Dopergin; ***Neth.:*** Dopergin; ***NZ:*** Dopergin; ***Spain:*** Dopergin; ***Switz.:*** Dopergin†; ***Thai.:*** Dopergin†; ***Turk.:*** Dopergin.

## Metixene Hydrochloride *(BANM, rINNM)*

Hidrocloruro de metixeno; Methixene Hydrochloride *(USAN)*; Methixene Hydrochloride Monohydrate; Metikseenihydrokloridi; Metikseno hidrochloridas; Métixène, chlorhydrate de; Metixén-hidroklorid; Metixen-hydrochlorid monohydrát; Metixenhydroklorid; Metixeni hydrochloridum; Metixeni Hydrochloridum Monohydricum; NSC-78194; SJ-1977. (*RS*)-9-(1-Methyl-3-piperidylmethyl)thioxanthene hydrochloride monohydrate.

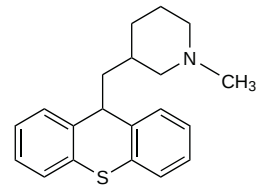
Метиксена Гидрохлорид

$C_{20}H_{23}NS,HCl,H_2O$ = 363.9.

*CAS — 4969-02-2 (metixene); 1553-34-0 (anhydrous metixene hydrochloride); 7081-40-5 (metixene hydrochloride monohydrate).*

*ATC — N04AA03.*

*ATC Vet — QN04AA03.*



*(metixene)*

**Pharmacopoeias.** In *Eur.* (see p.vii)

**Ph. Eur. 6.2** (Metixene Hydrochloride). A white or almost white, crystalline or fine crystalline powder. Soluble in water, in alcohol, and in dichloromethane. A 1.8% solution in water has a pH of 4.4 to 5.8. Protect from light.

### Profile

Metixene hydrochloride is a tertiary antimuscarinic with actions similar to those of atropine (p.1219); it also has antihistaminic and direct antispasmodic properties.

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. The usual oral dose of metixene hydrochloride is 2.5 mg three times daily initially, gradually increased according to response to a total of 15 to 60 mg daily in divided doses.

Metixene hydrochloride has also been used in preparations to relieve gastrointestinal spasms.

### Preparations

**Proprietary Preparations** (details are given in Part 3)

***Ger.:*** Tremarit; ***Hung.:*** Tremaril; ***Ital.:*** Tremaril; ***Swed.:*** Tremoquil†.

**Multi-ingredient:** ***Philipp.:*** Spasmo-Canulase; ***Port.:*** Espasmo Canulase; ***S.Afr.:*** Spasmo-Canulase; ***Switz.:*** Spasmo-Canulase.