claimed to be mainly effective against tremor. Bornaprine hydrochloride is given orally in initial doses of 2 mg daily gradually increased to 6 to 12 mg daily according to response. It is also used in the treatment of **hyperhidrosis** (p.1580) in a dose of 4 to 8 mg daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Sormodren; ***Ger.:*** Sormodren; ***Ital.:*** Sormodren; ***Turk.:*** Sormodren.

Bromocriptine Mesilate *(BANM, rINNM)*

Bromocriptine, mésilate de; Bromocriptine Mesylate *(USAN)*; Bromocriptine Methanesulphonate; Bromocriptini mesilas; Bromocryptine Mesylate; 2-Bromo-α-ergocryptine Mesylate; 2-Bromoergocryptine Monomethanesulfonate; Bromokriptiinimesilaatti; Bromokriptin Mesilat; Bromokriptinmesilat; Bromokriptin-mesylát; Brómokriptin-mezilát; Bromokriptino mesilatas; CB-154 (bromocriptine); Mesilato de bromocriptina. (5′*S*)-2-Bromo-12′-hydroxy-2′-(1-methylethyl)-5′-(2-methylpropyl)-ergotaman-3′,6′,18-trione methanesulphonate.

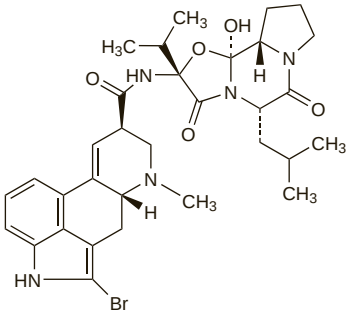
Бромокриптина Мезилат

$C_{32}H_{40}BrN_5O_5,CH_4O_3S$ = 750.7.

CAS — 25614-03-3 (bromocriptine); 22260-51-1 (bromocriptine mesilate).

ATC — G02CB01; N04BC01.

ATC Vet — QG02CB01; QN04BC01.



(bromocriptine)

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US*.
Ph. Eur. 6.2 (Bromocriptine Mesilate). A white or slightly coloured fine crystalline powder. Practically insoluble in water; soluble in alcohol; sparingly soluble in dichloromethane; freely soluble in methyl alcohol. A 1% solution in a mixture of 2 parts methyl alcohol to 8 of water has a pH of 3.1 to 3.8. Store in airtight containers at a temperature not exceeding −15°. Protect from light.
USP 31 (Bromocriptine Mesylate). A white or slightly coloured fine crystalline powder; odourless or having a weak characteristic odour. Store in airtight containers at a temperature not exceeding 8°. Protect from light.

Adverse Effects

Nausea is the most common adverse effect at the beginning of treatment with bromocriptine, but vomiting, dizziness, and orthostatic hypotension may also occur. Syncope has followed initial doses.

Adverse effects are generally dose-related and may therefore be more frequent with the higher doses that have been used in the treatment of parkinsonism and acromegaly. Reduction of the dosage, followed in a few days by a more gradual increase, may alleviate many adverse effects. Nausea may be reduced by taking bromocriptine with food; domperidone may also be given at least 1 hour before bromocriptine, for the first few days of therapy.

Bromocriptine and similar drugs are vasoconstrictors; Raynaud's syndrome or digital vasospasm, induced by cold, and leg cramps have been reported. Other cardiovascular effects have included erythromelalgia, prolonged severe hypotension, arrhythmias, and exacerbation of angina. Very rarely hypertension, myocardial infarction, seizures or stroke (both sometimes preceded by severe headache or visual disturbances), and psychiatric disorders have been reported in postpartum women given bromocriptine.

The use of ergot derivatives such as bromocriptine has been associated with retroperitoneal fibrosis, pleural thickening and effusions, and pericarditis and pericardial effusions.

Other adverse effects reported include headache, nasal congestion, drowsiness, dry mouth, constipation, diarrhoea, and altered liver-function tests. Dyskinesias and psychomotor excitation have occurred in patients suffering from parkinsonism. Gastrointestinal bleeding has been reported in acromegalic patients. Psychosis, with hallucinations, delusions, and confusion, occurs particularly when high doses are used to treat parkinsonism, but has also been reported with low doses. A neuroleptic malignant-like syndrome associated with abrupt withdrawal of bromocriptine has been reported very rarely.

Incidence of adverse effects. In 27 published studies of the treatment of Parkinson's disease, 217 of the 790 patients given bromocriptine had adverse effects.[1] Mental changes were noted in 90 patients, dyskinesia in 20, orthostatic hypotension in 40, and gastrointestinal effects in 40. The fewest adverse effects (9%) occurred with low-dose bromocriptine, more occurred with high-dose bromocriptine (27%) or with low-dose bromocriptine with levodopa (26%), and the most occurred with high-dose bromocriptine and levodopa (32%). However, those on high doses had more advanced disease and might have been more susceptible to mental changes and dyskinesias.

An analysis by the manufacturer of published reports on patients treated with bromocriptine for 1 to 10 years concluded that in general, adverse effects noted were no different from those associated with short-term treatment.[2]

1. Lieberman AN, Goldstein M. Bromocriptine in Parkinson disease. *Pharmacol Rev* 1985; **37:** 217–27.
2. Weil C. The safety of bromocriptine in long-term use: a review of the literature. *Curr Med Res Opin* 1986; **10:** 25–51.

Effects on the blood. Severe leucopenia and mild thrombocytopenia developed in a 23-year-old woman after treatment with bromocriptine 7.5 to 10 mg daily for about 3 months.[1]

1. Giampietro O, *et al*. Severe leukopenia and mild thrombocytopenia after chronic bromocriptine (CB-154) administration. *Am J Med Sci* 1981; **281:** 169–72.

Effects on the cardiovascular system. An early review noted that asymptomatic **hypotension** occurred in many subjects given bromocriptine.[1] However, faintness and dizziness, sometimes accompanied by *nausea* and *vomiting*, were common at the start of treatment with bromocriptine and these symptoms rather than an anaphylactic type of reaction were likely to account for the collapse that occurred in a few sensitive patients. Two of 53 patients with Parkinson's disease fainted after an initial dose of 1.25 or 2.5 mg, but the exact incidence of shock-like syndromes was difficult to assess; the manufacturers had stated that 22 of over 10 000 subjects given bromocriptine had had hypotension and collapse, mainly at the start of treatment.

- All patients starting treatment should be warned of the possibility of fainting. The initial dose should not exceed 1.25 to 2.5 mg and should be taken with food and in bed.

If fainting does occur recovery is usually rapid and spontaneous. Tolerance to adverse effects such as hypotension and nausea may develop rapidly.

Hypertension, *seizures*, *stroke*, and *myocardial infarction* have been associated with bromocriptine therapy, notably in postpartum women.[2-4] A study involving 1813 women suggested that the risk of **postpartum hypertension** was increased in women who had pregnancy-induced hypertension and that this risk was further increased in those who took bromocriptine for suppression of lactation.[5] A case-controlled study[6] involving 43 of the women who had had postpartum seizures while taking bromocriptine found that while the initial risk of seizures appeared to be lower in patients taking bromocriptine there was a small positive association with seizures occurring more than 72 hours after delivery.

- Although a causal relationship between the use of bromocriptine and these adverse effects in postpartum women has not been established, licensed product information recommends that bromocriptine should not be used post partum or in the puerperium in women with high blood pressure, coronary artery disease or other severe cardiovascular disorders, or symptoms or history of serious psychiatric disorders.
- It is also recommended that when bromocriptine is used in postpartum women blood pressure should be carefully monitored, especially during the first few days and if hypertension, unremitting headache, or signs of CNS toxicity develop, treatment should be discontinued immediately.

Severe dilated **cardiomyopathy** has been reported in a patient being treated with bromocriptine for microprolactinoma.[7]

For details of **fibrotic reactions** resulting in cardiovascular adverse effects, see Fibrosis, below.

1. Parkes D. Side effects of bromocriptine. *N Engl J Med* 1980; **302:** 749–50.
2. Anonymous. Postpartum hypertension, seizures, strokes reported with bromocriptine. *FDA Drug Bull* 1984; **14:** 3.
3. Ruch A, Duhring JL. Postpartum myocardial infarction in a patient receiving bromocriptine. *Obstet Gynecol* 1989; **74:** 448–51.
4. Larrazet F, *et al*. Possible bromocriptine-induced myocardial infarction. *Ann Intern Med* 1993; **118:** 199–200.
5. Watson DL, *et al*. Bromocriptine mesylate for lactation suppression: a risk for postpartum hypertension? *Obstet Gynecol* 1989; **74:** 573–6.
6. Rothman KJ, *et al*. Bromocriptine and puerperal seizures. *Epidemiology* 1990; **1:** 232–8.
7. Kaushik P, *et al*. Acute onset of severe dilated cardiomyopathy during bromocriptine therapy. *Ann Pharmacother* 2004; **38:** 1219–21.

Effects on the ears. Audiometric evidence of bilateral sensorineural hearing loss was reported in 3 patients receiving bromocriptine 15 or 20 mg daily for chronic hepatic encephalopathy.[1] Hearing improved when the dose was reduced to 10 mg daily.

1. Lanthier PL, *et al*. Bromocriptine-associated ototoxicity. *J Laryngol Otol* 1984; **98:** 399–404.

Effects on electrolytes. There have been isolated reports of severe hyponatraemia associated with the use of bromocriptine.[1,2]

1. Marshall AW, *et al*. Bromocriptine-associated hyponatraemia in cirrhosis. *BMJ* 1982; **285:** 1534–5.
2. Damase-Michel C, *et al*. Hyponatraemia in a patient treated with bromocriptine. *Drug Invest* 1993; **5:** 285–7.

Effects on the eyes. Blurred vision and diplopia has been reported in several patients receiving bromocriptine.[1] Reversible myopia also developed in a patient with hyperprolactinaemia given bromocriptine.[2]

Licensed product information states that visual field impairment associated with macroprolactinoma usually resolves with bromocriptine treatment. However, in a patient with progressive visual loss due to compression of the optic chiasm by a large pituitary tumour, bromocriptine caused total visual loss within hours.[3] Vision slowly returned to normal when the patient was placed in the supine position; the most likely cause of the visual loss was thought to be orthostatic hypotension with resultant decrease in perfusion pressure to the visual system. Monitoring of visual fields is recommended in patients with macroprolactinoma.

Bromocriptine has been reported to cause visual cortical disturbances.[4] In some cases blurred vision and transient cortical blindness have preceded seizures and strokes.

1. Calne DB, *et al*. Long-term treatment of parkinsonism with bromocriptine. *Lancet* 1978; **i:** 735–7.
2. Manor RS, *et al*. Myopia during bromocriptine treatment. *Lancet* 1981; **i:** 102.
3. Couldwell WT, Weiss MH. Visual loss associated with bromocriptine. *Lancet* 1992; **340:** 1410–11.
4. Lane RJM, Routledge PA. Drug-induced neurological disorders. *Drugs* 1983; **26:** 124–47.

Effects on mental function. High doses of bromocriptine are well known to cause **psychotic reactions** in patients with parkinsonism.[1] However, mania has also been associated with the use of bromocriptine post partum[2,3] and it has been stated that psychological symptoms can occur with doses of only 2.5 to 5 mg daily.[4] It was also noted that, unlike the relatively mild and transient symptoms associated with levodopa, bromocriptine produces a severe psychosis in which the patient is violent and aggressive, suffering from intense delusions which are often hostile and violent; complete withdrawal of bromocriptine may still leave a residue of severe psychotic illness persisting for 1 to 3 weeks. Psychosis associated with low doses of bromocriptine has often occurred in patients with a history of psychotic illness or disturbances in behaviour and mood prior to treatment.[5-7] Drug-related psychotic reactions have also been reported in patients with no psychiatric history;[8,9] of 600 patients given bromocriptine or lisuride for the treatment of acromegaly or prolactinoma, 8 developed symptoms including anxiety, depression, auditory hallucinations, delusions, hyperactivity, disinhibition, euphoria, and insomnia and 4 had received doses only previously associated with psychosis in susceptible patients.[9]

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

For reports of **daytime somnolence** occurring in patients receiving dopamine agonists including bromocriptine, see under Levodopa, p.805.

1. Calne DB, *et al*. Long-term treatment of parkinsonism with bromocriptine. *Lancet* 1978; **i:** 735–7.
2. Vlissides DN, *et al*. Bromocriptine-induced mania? *BMJ* 1978; **1:** 510.
3. Brook NM, Cookson IB. Bromocriptine-induced mania? *BMJ* 1978; **1:** 790.
4. Pearce I, Pearce JMS. Bromocriptine in parkinsonism. *BMJ* 1978; **1:** 1402–4.
5. Pearson KC. Mental disorders from low-dose bromocriptine. *N Engl J Med* 1981; **305:** 173.
6. Le Feuvre CM, *et al*. Bromocriptine-induced psychosis in acromegaly. *BMJ* 1982; **285:** 1315.
7. Procter AW, *et al*. Bromocriptine induced psychosis in acromegaly. *BMJ* 1983; **286:** 50. Correction. *ibid.*; 311.
8. Einarson TR, Turchet EN. Psychotic reaction to low-dose bromocriptine. *Clin Pharm* 1983; **2:** 273–4.
9. Turner TH, *et al*. Psychotic reactions during treatment of pituitary tumours with dopamine agonists. *BMJ* 1984; **289:** 1101–3.

Effects on the nervous system. CSF rhinorrhoea has been associated with bromocriptine therapy in patients with invasive prolactinomas. A report of 3 cases found 13 further cases on re-

viewing the literature;[1] of these, 7 patients had developed rhinorrhoea within 1 month of starting bromocriptine and 2 cases developed after 12 months.

For reference to seizures associated with the use of bromocriptine in postpartum women, see Effects on the Cardiovascular System, above.

1. Barlas O, *et al.* Bromocriptine-induced cerebrospinal fluid fistula in patients with macroprolactinomas: report of three cases and a review of the literature. *Surg Neurol* 1994; **41:** 486–9.

Effects on the respiratory system. For reports of fibrotic reactions occurring in patients with Parkinson's disease receiving ergot derivative dopamine agonists including bromocriptine, see Fibrosis, below.

Effects on sexual function. For reports of the effects of dopamine agonists on sexual function, see under Levodopa, p.806.

Effects on the urinary tract. Constant dribbling urinary incontinence developed in a woman receiving bromocriptine 2.5 mg daily for a recurrent pituitary growth; symptoms resolved on stopping the drug and recurred on rechallenge.[1] Bromocriptine has been shown to have two effects, one on the bladder outflow tract and one on the detrusor muscle, that could predispose to urinary incontinence.[2]

1. Sandyk R, Gillman MA. Urinary incontinence in patient on long-term bromocriptine. *Lancet* 1983; **ii:** 1260–1.
2. Caine M. Bromocriptine and urinary incontinence. *Lancet* 1984; **i:** 228.

Fibrosis. Fibrosis has been associated with the long-term use of ergot derivatives (see under Methysergide, p.623). Fibrotic reactions such as cardiac valvulopathy and pleuropulmonary effusion have been reported with bromocriptine, cabergoline, lisuride, and pergolide therapy in patients with Parkinson's disease.

Constrictive pericarditis[1] was reported in 2 patients who had received *bromocriptine* for 2 and 4 years, respectively; the latter still had slight pleural effusion 13 months after the drug was stopped. Valvular heart disease[2] developed in another patient who had received bromocriptine for 5 years; symptoms resolved 6 months after stopping the drug. Interstitial lung disease, with dyspnoea, chest pain, cough, and pulmonary fibrosis was reported[3] in a patient after use of relatively high doses of bromocriptine (62 mg daily). Respiratory symptoms largely resolved on withdrawal of the drug, although functional respiratory changes and moderate dyspnoea persisted after 6 months. A review of the literature revealed several other reports of pleuropulmonary fibrosis associated with relatively high doses of bromocriptine which occurred after between 15 days and up to 3 years of treatment. Although the incidence of this effect did not seem to be high, similar cases have continued to be reported.[4-6] In June 2008 the EMEA recommended that for long-term use in conditions such as Parkinson's disease, the maximum dose should be 30 mg daily.[7]

A patient developed pleuropulmonary disease 16 months after starting treatment with *cabergoline*;[8] he had previously received bromocriptine for 10 years and had had a normal chest X-ray at the time of transfer to cabergoline treatment. In another report, 2 cases of pleural effusion/pulmonary fibrosis, occurring after 10 to 11 months of treatment, were described.[9] One patient had modest pretreatment lung alterations attributed to previous bromocriptine therapy. Withdrawal was associated with improvement in both cases. Congestive heart failure secondary to constrictive pericarditis, and severe pleuropulmonary fibrosis that resulted in dyspnoea, persistent in one case,[10] have also been reported in 2 patients receiving long-term cabergoline.[10,11] Another patient developed cardiac valvulopathy after taking cabergoline for a total of 20 months;[12] her dosage was 4 mg daily for the last 7 months. Cardiac symptoms slowly improved on withdrawal of the drug, although some evidence of valvular defects was still present 23 months later. Valvular heart disease has also been reported in a 74-year-old man after 4 months of therapy with cabergoline [dosage not stated].[13] By December 2005, 86 cases of suspected adverse reactions to cabergoline had been reported to the Australian Drug Reactions Advisory Committee (ADRAC),[14] of which 15 described pleural or pulmonary fibrosis/effusion, or pneumonitis; time to onset ranged from a few days to over 3 years with a median of 4 months. There had been no reports of fibrotic complications associated with low-dose cabergoline in the treatment of lactation suppression and hyperprolactinaemia. The UK MHRA considers the risk of cardiac valvulopathy to be high and UK labelling for cabergoline has been amended accordingly (see p.802) with the EMEA in June 2008 recommending a maximum dose of 3 mg daily.[7]

A woman developed bilateral pleural effusions after taking *lisuride* 4 mg daily for about 17 months.[8] Her condition improved on stopping lisuride.

The UK CSM[15] reported in 2003 that *pergolide* had been associated with cases of cardiac valvulopathy; since 1989, valvulopathy had been reported in fewer than 5 in 100 000 patients. The CSM also referred to a published case series[16] which reported on 3 patients with severe tricuspid regurgitation after long-term pergolide treatment. The authors of this case series and the CSM both considered that, based on the available evidence, there was a potential association between pergolide and cardiac valvulopathy. Subsequently, the FDA[17] stated that, up to the end of 2002, it was aware of 15 cases of valvular heart disease with pergolide treatment; this figure included the 3 cases reported in the above series and 4 cases from the UK. A later study[18] that examined 78 patients taking pergolide for Parkinson's disease found evidence of restrictive valvular heart disease in 15 of 52 (29%) patients taking doses less than 5 mg daily and in 11 of 26 (42%) receiving doses of 5 mg or more daily. Pulmonary fibrosis and retroperitoneal fibrosis have also been associated with pergolide treatment;[19-21] in most cases, symptoms improved when the drug was stopped. Duration of exposure to pergolide ranged from 6 months[20] to 11 years.[21]

In April 2002 the CSM[22] calculated crude reporting rates of fibrotic reactions associated with the ergot derivative dopamine agonists (bromocriptine, cabergoline, lisuride, and pergolide), based on data submitted to its Yellow Card scheme and estimated drug exposure. Pergolide was found to be associated with a higher reporting rate of fibrotic reactions compared with the other ergot derivatives; however, this result needed further investigation to see if it reflected a true increase in risk or was due to factors such as reporting biases. There is some evidence that the incidence of reactions to pergolide are dose-related, and doses are restricted in many countries (see p.812) and in June 2008 the EMEA recommended a maximum dose of 3 mg daily.[7] Pergolide was withdrawn from the market in the USA and Canada. It is recommended that baseline investigations such as erythrocyte sedimentation rate, urea and electrolyte concentrations, and a chest x-ray should be performed before starting treatment with this class of drugs.

1. Champagne S, *et al.* Chronic constrictive pericarditis induced by long-term bromocriptine therapy: report of two cases. *Ann Pharmacother* 1999; **33:** 1050–4.
2. Serratrice J, *et al.* Fibrotic valvular heart disease subsequent to bromocriptine treatment. *Cardiol Rev* 2002; **10:** 334–6.
3. Vergeret J, *et al.* Fibrose pleuro-pulmonaire et bromocriptine. *Sem Hop Paris* 1984; **60:** 741–4.
4. Kinnunen E, Viljanen A. Pleuropulmonary involvement during bromocriptine treatment. *Chest* 1988; **94:** 1034–6.
5. Macak IA, *et al.* Bromocriptine-induced pulmonary disease. *Can J Hosp Pharm* 1991; **44:** 37–8, xxiv.
6. Debove P, *et al.* Pleuropneumopathie à la bromocriptine chez un parkinsonien: revue de la littérature à propos d'une nouvelle observation. *Ann Med Interne (Paris)* 1998; **149:** 167–71.
7. EMEA. EMEA recommends new warnings and contraindications for ergot-derived dopamine agonists (issued 26th June, 2008). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/32239508en.pdf (accessed 08/08/08)
8. Bhatt MH, *et al.* Pleuropulmonary disease associated with dopamine agonist therapy. *Ann Neurol* 1991; **30:** 613–16.
9. Geminiani G, *et al.* Cabergoline in Parkinson's disease complicated by motor fluctuations. *Mov Disord* 1996; **11:** 495–500.
10. Ling LH, *et al.* Constrictive pericarditis and pleuropulmonary disease linked to ergot dopamine agonist therapy (cabergoline) for Parkinson's disease. *Mayo Clin Proc* 1999; **74:** 371–5.
11. Townsend M, MacIver DH. Constrictive pericarditis and pleuropulmonary fibrosis secondary to cabergoline treatment for Parkinson's disease. *Heart* 2004; **90:** e47.
12. Horvath J, *et al.* Severe multivalvular heart disease: a new complication of the ergot derivative dopamine agonists. *Mov Disord* 2004; **19:** 656–62.
13. Pinero A, *et al.* Cabergoline-related severe restrictive mitral regurgitation. *N Engl J Med* 2005; **353:** 1976–7.
14. Australian Adverse Drug Reactions Advisory Committee (ADRAC). Ergot derivatives and fibrotic reactions. *Aust Adverse Drug React Bull* 2006; **25:** 3. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0602.pdf (accessed 30/05/08)
15. Committee on Safety of Medicines/Medicines and Healthcare products Regulatory Agency. Pergolide (Celance) and cardiac valvulopathy. *Current Problems* 2003; **29:** 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007450&RevisionSelectionMethod=LatestReleased (accessed 16/02/06)
16. Pritchett AM, *et al.* Valvular heart disease in patients taking pergolide. *Mayo Clin Proc* 2002; **77:** 1280–6.
17. Flowers CM, *et al.* The US Food and Drug Administration's registry of patients with pergolide-associated valvular heart disease. *Mayo Clin Proc* 2003; **78:** 730–1.
18. Van Camp G, *et al.* Treatment of Parkinson's disease with pergolide and relation to restrictive valvular heart disease. *Lancet* 2004; **363:** 1179–83.
19. Agarwal P, *et al.* Diagnosis and management of pergolide-induced fibrosis. *Mov Disord* 2004; **19:** 699–704.
20. Simcock D, Paviour D. Rapid onset of pergolide-induced pulmonary fibrosis in a patient with corticobasal degeneration. *Hosp Med* 2004; **65:** 372–3.
21. Tintner R, *et al.* Pleuropulmonary fibrosis after long-term treatment with the dopamine agonist pergolide for Parkinson disease. *Arch Neurol* 2005; **62:** 1290–5.
22. Committee on Safety of Medicines/Medicines Control Agency. Fibrotic reactions with pergolide and other ergot-derived receptor agonists. *Current Problems* 2002; **28:** 3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007454&RevisionSelectionMethod=LatestReleased (accessed 16/02/06)

Hypersensitivity. An allergic reaction developed in a 26-year-old woman being treated with bromocriptine for a prolactin-secreting microadenoma.[1] The patient reacted similarly to lisuride and treatment was continued with quinagolide.

1. Merola B, *et al.* Allergy to ergot-derived dopamine agonists. *Lancet* 1992; **339:** 620.

Oedema. Oedema poorly responsive to diuretics has been reported[1] in a patient given bromocriptine as part of treatment for prolactinoma. The oedema improved on substitution of pergolide but worsened with higher doses. Oedema resolved when treatment was changed to quinagolide. The reaction was considered to be idiosyncratic since enquiries by the author of the report had revealed only one similar case. In a subsequent report[2] a patient with Parkinson's disease who had been receiving bromocriptine for 5 years developed marked lower leg oedema, and subsequently cough, dyspnoea, and chest pain associated with an exudative pleural effusion; there was no evidence of fibrosis. Both oedema and effusion had largely resolved within 4 weeks of stopping bromocriptine.

1. Blackard WG. Edema—an infrequently recognized complication of bromocriptine and other ergot dopaminergic drugs. *Am J Med* 1993; **94:** 445.
2. Messiaen T, *et al.* Épanchement pleural et importants œdèmes des membres inférieurs induits par la bromocriptine. *Rev Med Interne* 1996; **17:** 680–3.

Overdosage. The most striking symptom in two children aged 2 and 2½ years who accidentally ingested an estimated 25 and 7.5 mg of bromocriptine, respectively, was lethargy with altered mental status.[1] The first child vomited and became sleepy. On admission he was markedly lethargic, but combative when disturbed, and also had hypotension, shallow breathing, dilated pupils, and hyperreflexic lower extremities. Nasogastric lavage was promptly performed, and activated charcoal and then magnesium citrate given. Blood pressure and ECG were monitored, and glucose and sodium chloride solution infused. The other child vomited, became lethargic, and had dilated pupils. Ipecacuanha was given, and activated charcoal followed by magnesium citrate given by nasogastric tube. Both children recovered completely.

1. Vermund SH, *et al.* Accidental bromocriptine ingestion in childhood. *J Pediatr* 1984; **105:** 838–40.

Withdrawal syndromes. Transient galactorrhoea and hyperprolactinaemia occurred in a young woman after withdrawal of bromocriptine therapy for Parkinson's disease.[1] It was suggested the effects were due to a rebound phenomenon. For discussion of a syndrome resembling neuroleptic malignant syndrome that has developed on withdrawal of bromocriptine and other antiparkinsonian drugs, see under Levodopa, p.806.

1. Pentland B, Sawers JSA. Galactorrhoea after withdrawal of bromocriptine. *BMJ* 1980; **281:** 716.

Precautions

Patients with hyperprolactinaemia should be investigated for the possibility of a pituitary tumour before treatment with bromocriptine. Malignancy must be excluded in patients with cyclical benign breast disorders such as mastalgia. Annual gynaecological examinations (or every 6 months for postmenopausal women) are recommended. Treatment of women with hyperprolactinaemic amenorrhoea results in ovulation; patients not wishing to conceive should be advised to use contraceptive measures although oral contraceptives should be avoided because they may increase prolactin levels. Acromegalic patients should be checked for symptoms of peptic ulceration before therapy and should immediately report symptoms of gastrointestinal discomfort during therapy.

In general, bromocriptine should be given with caution to patients with cardiovascular disease, Raynaud's syndrome, or a history of psychosis. It is contra-indicated in patients with hypersensitivity to bromocriptine or other ergot alkaloids, and in those with uncontrolled hypertension.

Bromocriptine is contra-indicated in the toxaemia of pregnancy. It should also not be used postpartum or in the puerperium in women with hypertension, coronary artery disease, or symptoms or a history of serious psychiatric disorders. When used, blood pressure should be monitored carefully, especially during the first few days in postpartum women. Particular caution is necessary in patients who are receiving or who have recently received drugs that can alter blood pressure; use with ergot alkaloids during the puerperium is not recommended. Treatment in postpartum women should be stopped immediately if hypertension, unremitting headache, or signs of CNS toxicity develop.

Hypotensive reactions may be disturbing in some patients during the first few days of treatment and those who drive or operate machinery should be warned of the possibility of dizziness and fainting during this period. Excessive daytime sleepiness and sudden onset of sleep may also occur with bromocriptine and other dopaminergic agonists, and caution is advised when driving or operating machinery; patients who suffer such effects should not drive or operate machinery until the effects have stopped recurring. A reduction in dosage or withdrawal of the drug may be appropriate. Because of the risk of fibrosis bromocriptine is contra-indicated in patients with pre-existing valve problems.

Patients on long-term, high-dose therapy should be monitored for signs of progressive fibrotic disorders such as retroperitoneal fibrosis and bromocriptine withdrawn if fibrotic changes are diagnosed or suspected. It is recommended that baseline investigations such as erythrocyte sedimentation rate, urea and electrolyte concentrations, and a chest x-ray should be performed before starting treatment with bromocriptine. Periodic monitoring of cardiovascular, haematopoietic, hepatic, and renal function is also recommended. Monitoring of visual fields is recommended in patients with macroprolactinoma.

Breast feeding. The American Academy of Pediatrics[1] considers that bromocriptine should be given with caution to breast-feeding mothers, since it suppresses lactation and may be hazardous to the mother.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 16/02/06)

Porphyria. Bromocriptine is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Pregnancy. Details of various surveys of the effect of the use of bromocriptine during pregnancy have been published by the manufacturer.[1,2] The first survey was based on spontaneous reporting of all pregnancies between 1973 and 1980 in women who had taken bromocriptine after conception.[1] Information was obtained on 1410 pregnancies in 1335 women, the majority of whom had been treated for hyperprolactinaemic conditions, while in 256 pregnancies pituitary tumours and acromegaly were the primary diagnosis. Bromocriptine was generally taken at some time in the first 8 weeks after conception, the mean duration of treatment being 21 days. In 4 patients bromocriptine was not prescribed until late in pregnancy and in 9 with acromegaly and pituitary microadenoma it was taken continuously throughout gestation. There were 157 (11.1%) spontaneous abortions, 12 (0.9%) extrauterine pregnancies, 2 patients with 3 hydatidiform moles (0.2%), and an incidence of twin pregnancies of 1.8%. Major congenital abnormalities were detected in 12 (1%) infants at birth and minor abnormalities in 31 (2.5%). A second survey,[2] which consisted of formal monitoring of the use of bromocriptine at 33 clinics between 1979 and 1980, collected data on a further 743 pregnancies in 668 women and had similar findings. The incidence rates reported in these surveys were comparable with those quoted for normal populations and the data indicate that the use of bromocriptine in the treatment of women with infertility is not associated with an increased risk of abortion, multiple pregnancy, or congenital abnormalities. Furthermore, follow-up, for up to 9 years, of 546 children exposed to bromocriptine *in utero* found no evidence that bromocriptine had any adverse effect on postnatal development.[2] Nevertheless, since the risk of abortion is not increased by interruption of treatment, licensed drug information recommends that bromocriptine therapy be stopped as soon as pregnancy is confirmed unless there is a definite indication for its continuation.

See also Pregnancy under Hyperprolactinaemia and Prolactinomas, below.

1. Turkalj I, *et al.* Surveillance of bromocriptine in pregnancy. *JAMA* 1982; **247:** 1589–91.
2. Krupp P, Monka C. Bromocriptine in pregnancy: safety aspects. *Klin Wochenschr* 1987; **65:** 823–7.

Interactions

Dopamine antagonists such as the phenothiazines, butyrophenones, thioxanthenes, and metoclopramide (but see below) might be expected to reduce the prolactin-lowering and the antiparkinsonian effects of bromocriptine and domperidone might reduce its prolactin-lowering effect. Memantine may enhance the effects of bromocriptine. Stimulants of gastrointestinal motility such as macrolide antibacterials or octreotide can increase the bioavailability of bromocriptine.

Alcohol. Alcohol intolerance was noted in 5 of 73 patients receiving bromocriptine 10 to 60 mg daily for the treatment of acromegaly.[1] Two patients who had gastrointestinal adverse effects while taking low doses of bromocriptine had a marked reduction in their symptoms and were able to tolerate higher doses when they refrained completely from alcohol.[2]

1. Wass JAH, *et al.* Long-term treatment of acromegaly with bromocriptine. *BMJ* 1977; **1:** 875–8.
2. Ayres J, Maisey MN. Alcohol increases bromocriptine's side effects. *N Engl J Med* 1980; **302:** 806.

Antibacterials. Drowsiness, dystonia, choreoathetoid dyskinesias, and visual hallucinations occurred when *josamycin* was given to a patient receiving bromocriptine.[1]

The systemic bioavailability of a single oral dose of bromocriptine 5 mg was markedly increased in 5 healthy subjects after treatment with *erythromycin estolate* 250 mg four times daily for 4 days;[2] clearance of bromocriptine was decreased and peak plasma concentrations of bromocriptine were more than 4 times higher than when given alone.

1. Montastruc JL, Rascol A. Traitement de la maladie de Parkinson par doses élevées de bromocriptine: interaction possible avec la josamycine. *Presse Med* 1984; **13:** 2267–8.
2. Nelson MV, *et al.* Pharmacokinetic evaluation of erythromycin and caffeine administered with bromocriptine. *Clin Pharmacol Ther* 1990; **47:** 694–7.

Antifungals. The response to bromocriptine was blocked in a patient who was also receiving *griseofulvin*.[1]

1. Schwinn G, *et al.* Metabolic and clinical studies on patients with acromegaly treated with bromocriptine over 22 months. *Eur J Clin Invest* 1977; **7:** 101–7.

Antipsychotics. Serum concentrations of prolactin rose and visual fields deteriorated when *thioridazine* was given to a 40-year-old man receiving bromocriptine therapy for a large prolactinoma.[1]

For a discussion of the effect of bromocriptine on patients receiving antipsychotics, see Antiparkinsonian Drugs under Chlorpromazine on p.974.

1. Robbins RJ, *et al.* Interactions between thioridazine and bromocriptine in a patient with a prolactin-secreting pituitary adenoma. *Am J Med* 1984; **76:** 921–3.

Metoclopramide. As noted in Interactions, above, there are theoretical reasons to suppose that dopamine antagonists such as metoclopramide might reduce the effects of bromocriptine. However, an early study[1] in 10 patients with Parkinson's disease given single doses of bromocriptine 12.5 to 100 mg found that pretreatment with metoclopramide 60 mg had no consistent effect upon plasma concentrations of bromocriptine or growth hormone and no consistent effect upon clinical response.

1. Price P, *et al.* Plasma bromocriptine levels, clinical and growth hormone responses in parkinsonism. *Br J Clin Pharmacol* 1978; **6:** 303–9.

Sympathomimetics. There have been isolated reports[1,2] of severe hypertension, with headache and life-threatening complications, in patients taking bromocriptine with *isometheptene mucate* or *phenylpropanolamine*.

1. Kulig K, *et al.* Bromocriptine-associated headache: possible life-threatening sympathomimetic interaction. *Obstet Gynecol* 1991; **78:** 941–3.
2. Chan JCN, *et al.* Postpartum hypertension, bromocriptine and phenylpropanolamine. *Drug Invest* 1994; **8:** 254–6.

Pharmacokinetics

Bromocriptine is rapidly absorbed from the gastrointestinal tract and peak plasma concentrations are achieved within 1 to 3 hours after oral doses. However, only about 30% of an oral dose is absorbed and, owing to extensive first-pass metabolism, the bioavailability is only about 6%. It has been reported to be 90 to 96% bound to serum albumin *in vitro*. It is metabolised in the liver, mainly by hydrolysis to lysergic acid and peptides. The elimination of bromocriptine is biphasic; half-lives of about 4 to 4.5 hours and 15 hours, respectively have been reported for the 2 phases. It is excreted mainly in faeces via the bile, with small amounts in urine.

◊ In a study involving 10 patients with Parkinson's disease, single oral doses of bromocriptine 12.5, 25, 50, and 100 mg resulted in very variable peak plasma concentrations ranging from 1.3 to 5.3, 1.4 to 3.5, 2.6 to 19.7, and 6.5 to 24.6 nanograms/mL, respectively, 30 to 210 minutes (mean 102 minutes) after dosage.[1] After 4 hours plasma concentrations were about 75% of the peak values. Clinical improvement was evident within 30 to 90 minutes of a dose with peak effect at about 130 minutes and in most patients improvement persisted throughout the 4-hour study period. Peak clinical response, peak fall in blood pressure, and peak rise in plasma concentrations of growth hormone occurred about 30, 60, and 70 minutes, respectively after peak plasma-bromocriptine concentrations but there was no significant relationship between them. However, there was a significant relationship between plasma concentrations and concurrent changes in clinical response compared with pretreatment scores. Dyskinesias occurred within 90 to 180 minutes of dosage in 5 of 10 patients.

Bromocriptine is well absorbed from standard oral tablets placed in the vagina and plasma concentrations sufficient to lower plasma prolactin concentrations have been achieved using this route.[2,3]

1. Price P, *et al.* Plasma bromocriptine levels, clinical and growth hormone responses in parkinsonism. *Br J Clin Pharmacol* 1978; **6:** 303–9.
2. Vermesh M, *et al.* Vaginal bromocriptine: pharmacology and effect on serum prolactin in normal women. *Obstet Gynecol* 1988; **72:** 693–8.
3. Katz E, *et al.* Successful treatment of a prolactin-producing pituitary macroadenoma with intravaginal bromocriptine mesylate: a novel approach to intolerance of oral therapy. *Obstet Gynecol* 1989; **73:** 517–20.

Uses and Administration

Bromocriptine, an ergot derivative (p.2010), is a dopamine D_2-agonist. It inhibits the secretion of prolactin (p.2017) from the anterior pituitary and is used in the treatment of prolactinoma and endocrinological disorders associated with hyperprolactinaemia, including amenorrhoea, galactorrhoea, hypogonadism, and infertility in both men and women. Bromocriptine 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 may be adequately relieved with simple analgesics and breast support. Growth hormone secretion may be suppressed by bromocriptine in some patients with acromegaly. Because of its dopaminergic activity bromocriptine is also used in the management of Parkinson's disease.

Bromocriptine is usually given orally as the mesilate; doses are expressed in terms of the base. Bromocriptine mesilate 2.87 mg is equivalent to about 2.5 mg of bromocriptine. Oral doses should be taken with food. Bromocriptine mesilate has also been given intramuscularly as a depot injection for disorders associated with hyperprolactinaemia.

For the **prevention of puerperal lactation** bromocriptine 2.5 mg is given on the day of delivery followed by 2.5 mg twice daily for 14 days. The risk of hypotension and, more rarely, hypertension must be borne in mind and it has been recommended that bromocriptine should not be given until at least 4 hours after delivery. For the **suppression of established lactation** it is given in a dose of 2.5 mg daily for 2 to 3 days subsequently increased to 2.5 mg twice daily for 14 days.

For the treatment of other conditions (see below) the dose of bromocriptine is usually increased gradually. In the UK, typically, an initial dose of 1 to 1.25 mg at night is given, increased to 2 to 2.5 mg at night after 2 to 3 days, and subsequently increased by 1 mg every 2 to 3 days to a dose of 2.5 mg twice daily, or more if necessary. In the USA, a usual starting dose is 1.25 to 2.5 mg daily increased by 2.5 mg every 2 to 7 days.

In the **treatment of hypogonadism and galactorrhoea syndromes and infertility** bromocriptine is introduced gradually as described above. Most patients with hyperprolactinaemia respond to 7.5 mg daily but up to 30 mg daily may be required. Infertile patients without raised serum concentrations of prolactin are usually given 2.5 mg twice daily. In patients known to have **prolactinomas** the dose is also introduced gradually as described above and may then be increased further by 2.5 mg every 2 to 3 days to a dose of 5 mg every 6 hours but occasionally patients may require up to 30 mg daily. Although unlicensed in the UK and USA, bromocriptine is used in some countries for **cyclical benign breast and menstrual disorders**. In benign breast disease bromocriptine is introduced gradually up to a daily dosage of 5 to 7.5 mg if necessary. In the treatment of premenstrual symptoms therapy should begin on day 14 of the cycle and introduced gradually up to a usual dosage of 2.5 mg twice daily until menstruation begins.

Bromocriptine may be used as an adjunct to surgery and radiotherapy to reduce plasma-growth hormone concentrations in **acromegalic patients**. In the UK, it is introduced gradually as described above and may then be increased further by 2.5 mg every 2 to 3 days if necessary up to 5 mg every 6 hours, according to response. In the USA, the usual starting dose (see above) may be increased by 1.25 to 2.5 mg every 3 to 7 days to a maximum daily dose of 100 mg if necessary; the usual dosage range is 20 to 30 mg daily.

In **Parkinson's disease** bromocriptine has been used alone, although it is usually given as an adjunct to levodopa treatment. It should be introduced even more gradually than the regimen above, and during this period patients already receiving levodopa can have their levodopa dosage decreased gradually until an optimal response is achieved. In the UK, a suggested initial

dose is the equivalent of 1 to 1.25 mg of bromocriptine at night during week 1, increased to 2 to 2.5 mg at night for week 2, 2.5 mg twice daily for week 3, and for week 4, 2.5 mg three times daily; the dose may be increased thereafter by 2.5 mg every 3 to 14 days according to response. The EMEA has recommended a maximum dose of 30 mg daily. In the USA, a usual starting dose is 1.25 to 2.5 mg twice daily increased by 2.5 mg every 14 to 28 days to a maximum dose of 100 mg daily if necessary.

Acromegaly. Dopaminergics can produce a paradoxical reduction in growth hormone secretion and bromocriptine has been used in acromegaly (p.1798) as adjunctive therapy to surgery, radiotherapy, or somatostatin analogues to reduce circulating growth hormone levels. While it is less effective than somatostatin analogues, it can be given orally and is therefore more convenient to administer.

Cushing's syndrome. There have been occasional reports of benefit with the use of bromocriptine in the treatment of Cushing's syndrome (p.2344). Remission of ACTH-dependent Cushing's syndrome was maintained for 6 years by bromocriptine 2.5 mg twice daily in a patient who had initially received pituitary irradiation.[1] However, the same group subsequently reported that they had found that bromocriptine did not effectively reduce ACTH secretion following bilateral adrenalectomy.[2]

1. Atkinson AB, *et al.* Six year remission of ACTH-dependent Cushing's syndrome using bromocriptine. *Postgrad Med J* 1985; **61:** 239–42.
2. Atkinson AB. The treatment of Cushing's syndrome. *Clin Endocrinol (Oxf)* 1991; **34:** 507–13.

Hepatic encephalopathy. For the view that the evidence does not support the use of dopaminergics such as bromocriptine in the management of hepatic encephalopathy see p.1697.

Hyperprolactinaemia and prolactinomas. Prolactinomas (prolactin-secreting pituitary adenomas) are among the commonest causes of hyperprolactinaemia. Raised serum-prolactin concentrations can result in reduced gonadotrophin production, which in turn may suppress gonadal function. Consequences may include oligomenorrhoea or amenorrhoea, and infertility in either sex. Galactorrhoea may also result from high prolactin levels and can occur in men as well as women.

Dopamine is the major inhibitory factor in the hypothalamus and directly inhibits the secretion of prolactin. Bromocriptine, a dopamine agonist, has been the first choice of treatment in many centres for the treatment of hyperprolactinaemia secondary to a prolactinoma although cabergoline is now preferred by some. Bromocriptine is extremely effective in controlling elevated circulating prolactin concentrations and restoring gonadal function; although it is rarely curative, it may produce considerable shrinkage of the adenoma.[1]

The sensitivity of hyperprolactinaemia to bromocriptine therapy can vary considerably between patients and this is reflected in the wide range of oral doses required to reduce prolactin concentrations to normal levels. Although beginning therapy with gradually increasing doses can minimise adverse effects it has been reported that about 5 to 10% of patients are unable to tolerate oral bromocriptine;[2] other dosage routes have therefore been investigated. Bromocriptine is well absorbed from standard oral tablets placed in the vagina and appears to be both effective in lowering prolactin concentrations and well tolerated when given by this route.[3] However, limitations are considered to be the relatively short duration of action and the relatively low dose that can be given.[2] A depot preparation given intramuscularly in a dose of 50 to 250 mg monthly has been found to be effective and well tolerated in long-term studies;[4,5] it is reported to be used in some centres to begin treatment for macroprolactinomas.[2]

For discussions of the management of hyperprolactinaemia and associated disorders see p.2079 (hyperprolactinaemia), p.2078 (amenorrhoea), p.2079 (hypogonadism), p.2179 (erectile dysfunction), and p.2080 (infertility).

1. Molitch ME. Medical management of prolactin-secreting pituitary adenomas. *Pituitary* 2002; **5:** 55–65.
2. Ciccarelli E, Camanni F. Diagnosis and drug therapy of prolactinoma. *Drugs* 1996; **51:** 954–65.
3. Ginsburg J, *et al.* Vaginal bromocriptine. *Lancet* 1991; **338:** 1205–6.
4. Ciccarelli E, *et al.* Long term therapy of patients with macroprolactinoma using repeatable injectable bromocriptine. *J Clin Endocrinol Metab* 1993; **76:** 484–8.
5. Ciccarelli E, *et al.* Double blind randomized study using oral or injectable bromocriptine in patients with hyperprolactinaemia. *Clin Endocrinol (Oxf)* 1994; **40:** 193–8.

PREGNANCY. References to the management of prolactinoma during pregnancy.[1-3] Bromocriptine has been successfully used for management in pregnant women, particularly if there is symptomatic enlargement of the tumour, although there continues to be debate on the appropriateness of continuous therapy in less high-risk individuals.

1. Randeva HS, *et al.* Prolactinoma and pregnancy *Br J Obstet Gynaecol* 2000; **107:** 1064–8.
2. Bronstein MD, *et al.* Medical management of pituitary adenomas: the special case of management of the pregnant woman. *Pituitary* 2002; **5:** 99–107.
3. Chiodini I, Liuzzi A. PRL-secreting pituitary adenomas in pregnancy. *J Endocrinol Invest* 2003; **26:** 96–9.

Lactation inhibition. Because of its effects on prolactin, bromocriptine is a potent suppressor of lactation and has been widely used for the prevention of lactation in women who choose not to breast feed post partum. However, bromocriptine has been associated with severe adverse effects in some women, and its use to suppress a physiological state has been criticised (see p.2003). Consequently, licensed product information from a number of countries recommends that bromocriptine should only be used to suppress puerperal lactation for medical reasons; it is also not recommended for the treatment of postpartum breast pain and engorgement that may be adequately relieved with simple analgesics and breast support.

Mastalgia. Since mastalgia (p.2092) can improve spontaneously, treatment should rarely be considered unless pain has been present for about 6 months. Bromocriptine is one of the drugs that may be used to treat mastalgia.[1,2] It may improve symptoms in up to about 50% of patients with cyclical mastalgia, but is less effective in the non-cyclical form.[3,4] Adverse effects can be severe in some patients.

1. Gateley CA, Mansel RE. Management of the painful and nodular breast. *Br Med Bull* 1991; **47:** 284–94.
2. Anonymous. Cyclical breast pain—what works and what doesn't. *Drug Ther Bull* 1992; **30:** 1–3.
3. Pye JK, *et al.* Clinical experience of drug treatments for mastalgia. *Lancet* 1985; **ii:** 373–7.
4. Mansel RE, Dogliotti L. European multicentre trial of bromocriptine in cyclical mastalgia. *Lancet* 1990; **335:** 190–3.

Neuroleptic malignant syndrome. Bromocriptine has been used in doses of up to 30 mg daily,[1-6] usually alone or with dantrolene, in the treatment of neuroleptic malignant syndrome (p.972) although some workers have not found it to be of use.[7]

1. Mueller PS, *et al.* Neuroleptic malignant syndrome: successful treatment with bromocriptine. *JAMA* 1983; **249:** 386–8.
2. Dhib-Jalbut S, *et al.* Treatment of the neuroleptic malignant syndrome with bromocriptine. *JAMA* 1983; **250:** 484–5.
3. Clarke CE, *et al.* Clinical spectrum of neuroleptic malignant syndrome. *Lancet* 1988; **ii:** 969–70.
4. Guerrero RM, Shifrar KA. Diagnosis and treatment of neuroleptic malignant syndrome. *Clin Pharm* 1988; **7:** 697–701.
5. Lo TCM, *et al.* Neuroleptic malignant syndrome: another medical cause of acute abdomen. *Postgrad Med J* 1989; **65:** 653–5.
6. Chandran GJ, *et al.* Neuroleptic malignant syndrome: case report and discussion. *Can Med Assoc J* 2003; **169:** 439–42.
7. Rosebush PI, *et al.* The treatment of neuroleptic malignant syndrome: are dantrolene and bromocriptine useful adjuncts to supportive care? *Br J Psychiatry* 1991; **159:** 709–12.

Parkinsonism. Dopamine agonists such as bromocriptine are often used to begin treatment of parkinsonism (p.791), particularly in younger patients, in an attempt to delay therapy with levodopa. They also have an adjunctive use when levodopa is no longer effective alone or cannot be tolerated and may sometimes be useful in reducing 'off' periods with levodopa and in ameliorating other fluctuations of mobility in the later stage of the disease. However, in early disease, there is no evidence that adjunctive bromocriptine prevents or delays the onset of motor complications associated with levodopa monotherapy.

References.

1. Temlett JA, *et al.* Adjunctive therapy with bromocriptine in Parkinson's disease. *S Afr Med J* 1990; **78:** 680–5.
2. Hely MA, *et al.* The Sydney Multicentre Study of Parkinson's disease: a randomised, prospective five year study comparing low dose bromocriptine with low dose levodopa-carbidopa. *J Neurol Neurosurg Psychiatry* 1994; **57:** 903–10.
3. Montastruc JL, *et al.* A randomised controlled study comparing bromocriptine to which levodopa was later added, with levodopa alone in previously untreated patients with Parkinson's disease: a five year follow up. *J Neurol Neurosurg Psychiatry* 1994; **57:** 1034–8.
4. Giménez-Roldán S, *et al.* Early combination of bromocriptine and levodopa in Parkinson's disease: a prospective randomized study of two parallel groups over a total follow-up period of 44 months including an initial 8-month double-blind stage. *Clin Neuropharmacol* 1997; **20:** 67–76.
5. Ogawa N, *et al.* Nationwide multicenter prospective study on the long-term effects of bromocriptine for Parkinson's disease: final report of a ten-year follow-up. *Eur Neurol* 1997; **38** (suppl 2): 37–49.
6. Lees AJ, *et al.* Ten-year follow-up of three different initial treatments in de-novo PD: a randomized trial. *Neurology* 2001; **57:** 1687–94.
7. van Hilten JJ, *et al.*. Bromocriptine versus levodopa in early Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 30/05/08).
8. van Hilten JJ, *et al.* Bromocriptine/levodopa combined versus levodopa alone for early Parkinson's disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 30/05/08).

Polycystic ovary syndrome. Bromocriptine has been tried in women with the polycystic ovary syndrome (p.2080) who have mild basal hyperprolactinaemia without evidence of a pituitary tumour.

Restless legs syndrome. The aetiology of restless legs syndrome (see Sleep-associated Movement Disorders, p.958) is obscure and treatment has largely been empirical but dopaminergic therapy has emerged as a common first-line choice. Bromocriptine showed some benefit in a small study.[1]

1. Walters AS, *et al.* A double-blind randomized crossover trial of bromocriptine and placebo in restless legs syndrome. *Ann Neurol* 1988: **24:** 455–8.

Withdrawal syndromes. ***ALCOHOL.*** Studies of the efficacy of bromocriptine as an aid in the maintenance of abstinence from alcohol (p.1626) have yielded conflicting results.[1-4] However, it has been suggested[3] that response to bromocriptine might be linked to a specific genotype of the D_2 dopamine receptor.

1. Dongier M, *et al.* Bromocriptine in the treatment of alcohol dependence. *Alcohol Clin Exp Res* 1991; **15:** 970–7.
2. Naranjo CA, *et al.* Long-acting bromocriptine (B) does not reduce relapse in alcoholics. *Clin Pharmacol Ther* 1995; **57:** 161.
3. Lawford BR, *et al.* Bromocriptine in the treatment of alcoholics with the D dopamine receptor A1 allele. *Nat Med* 1995; **1:** 337–41.
4. Powell BJ, *et al.* A double-blind, placebo-controlled study of nortriptyline and bromocriptine in male alcoholics subtyped by comorbid psychiatric disorders. *Alcohol Clin Exp Res* 1995; **19:** 462–8.

Preparations

BP 2008: Bromocriptine Capsules; Bromocriptine Tablets;
USP 31: Bromocriptine Mesylate Capsules; Bromocriptine Mesylate Tablets.

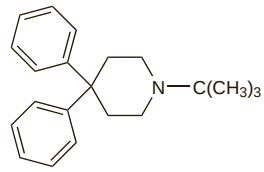
Proprietary Preparations (details are given in Part 3)
Arg.: Parlodel; Serocryptin†; ***Austral.:*** Bromohexal; Bromolactin†; Kripton; Parlodel; ***Austria:*** Bromed; Cehapark; Parlodel; Umprel; ***Belg.:*** Parlodel; ***Braz.:*** Bagren; Parlodel; ***Canad.:*** Parlodel; ***Chile:*** Criten; Grifocriptina; Kriptonal; Parlodel; Prigost; ***Cz.:*** Medocriptine; Parlodel; Serocryptin†; ***Denm.:*** Bromergon†; Parlodel; ***Fin.:*** Parlodel; ***Fr.:*** Bromo-Kin; Parlodel; ***Ger.:*** Bromocrel†; kirim; kirim gyn; Pravidel; ***Gr.:*** Parlodel; ***Hong Kong:*** Bromtine; Medocriptine; Parlodel; Serocryptin†; ***Hung.:*** Serocryptin†; ***India:*** Sicriptin; ***Indon.:*** Cripsa; Parlodel; ***Irl.:*** Parlodel; ***Israel:*** Parilac; Parlodel; ***Ital.:*** Parlodel; ***Malaysia:*** Butin†; Criptamine†; Medocriptine; Parlodel; Zolac†; ***Mex.:*** Broptin; Crilem; Cryocriptina; Kriptiser; Mesiken; Parlodel; Serocryptin†; ***Neth.:*** Parlodel; ***Norw.:*** Parlodel; ***Philipp.:*** Parlodel; Provasyn; ***Pol.:*** Bromergon; Bromocorn; Ergolaktyna; Parlodel; ***Port.:*** Parlodel; ***Rus.:*** Bromergon (Бромэргон); Parlodel (Парлодел); ***S.Afr.:*** Parlodel; ***Singapore:*** Butin†; Parlodel; Suplac†; ***Spain:*** Parlodel; ***Swed.:*** Pravidel; ***Switz.:*** Parlodel; ***Thai.:*** Brocaden; Bromergon; Parlodel; Suplac; ***Turk.:*** Gynodel; Parlodel; ***UAE:*** Antiprotin; ***UK:*** Parlodel; ***USA:*** Parlodel; ***Venez.:*** Parlodel; Serocryptin†.

Budipine *(rINN)*

Budipino; Budipinum. 1-*tert*-Butyl-4,4-diphenylpiperidine.

Будипин

$C_{21}H_{27}N$ = 293.4.
CAS — 57982-78-2.
ATC — N04BX03.
ATC Vet — QN04BX03.



Profile

Budipine is a phenylpiperidine derivative used as an adjunct in the treatment of parkinsonism (p.791). It is given orally as the hydrochloride in daily doses of up to 60 mg.

◊ References.

1. Spieker S, *et al.* Tremorlytic activity of budipine: a quantitative study with long-term tremor recordings. *Clin Neuropharmacol* 1995; **18:** 266–72.
2. Groen H, *et al.* A study to investigate the pharmacokinetics and metabolism of budipine after administration of a single oral dose of [C]-B757-01 to six healthy volunteers. *Br J Clin Pharmacol* 1999; **48:** 771P–772P.
3. Malsch U, *et al.* Monotherapie der Parkinsonschen Erkrankung mit Budipin: ein randomisierter Doppelblindvergleich mit Amantadin. *Fortschr Neurol Psychiatr* 2001; **69:** 86–9.
4. Przuntek H, *et al.* Budipine provides additional benefit in patients with Parkinson disease receiving a stable optimum dopaminergic drug regimen. *Arch Neurol* 2002; **59:** 803–6.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Parkinsan.