Profile
Aminotadalafil is an analogue of tadalafil (p.2196) that has been used in various preparations or dietary supplements and illegally promoted in some countries for the management of erectile dysfunction.

Dapoxetine Hydrochloride *(USAN, rINNM)*

Dapoxétine, Chlorhydrate de; Dapoxetini Hydrochloridum; Hidrocloruro de dapoxetina; LY-210448 (dapoxetine). (+)-(*S*)-*N*,*N*-Dimethyl-alpha-[2-(1-naphthyloxy)ethyl]benzylamine hydrochloride.

Дапоксетина Гидрохлорид

$C_{21}H_{23}NO, HCl = 341.9$.

CAS — 119356-77-3 (dapoxetine); 129938-20-1 (dapoxetine hydrochloride).

Profile
Dapoxetine hydrochloride is a rapidly absorbed short-acting SSRI being investigated specifically for on-demand treatment of premature ejaculation (p.2181).

◊ References.

1. Pryor JL, *et al.* Efficacy and tolerability of dapoxetine in treatment of premature ejaculation: an integrated analysis of two double-blind, randomised controlled trials. *Lancet* 2006; **368:** 929–37.
2. Modi NB, *et al.* Single- and multiple-dose pharmacokinetics of dapoxetine hydrochloride, a novel agent for the treatment of premature ejaculation. *J Clin Pharmacol* 2006; **46:** 301–9.
3. Andersson KE, *et al.* Pharmacokinetic and pharmacodynamic features of dapoxetine, a novel drug for 'on-demand' treatment of premature ejaculation. *BJU Int* 2006; **97:** 311–15.
4. Dresser MJ, *et al.* Pharmacokinetics of dapoxetine, a new treatment for premature ejaculation: impact of age and effects of a high-fat meal. *J Clin Pharmacol* 2006; **46:** 1023–9.

Darifenacin *(BAN, USAN, rINN)*

Darifenacina; Darifénacine; Darifenacinum; UK-88525. (*S*)-1-[2-(2,3-Dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-3-pyrrolidineacetamide.

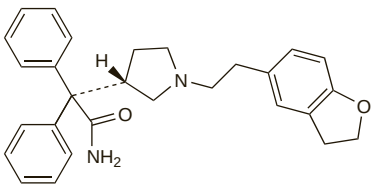
Дарифенацин

$C_{28}H_{30}N_2O_2 = 426.6$.

CAS — 133099-04-4.

ATC — G04BD10.

ATC Vet — QG04BD10.



Darifenacin Hydrobromide *(BANM, USAN, rINNM)*

Darifénacine, Bromhydrate de; Darifenacini Hydrobromidum; Hidrobromuro de darifenacina; UK-88525-04. (*S*)-2-{1-[2-(2,3-Dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidnyl}-2,2-diphenylacetamide hydrobromide.

Дарифенацина Гидробромид

$C_{28}H_{30}N_2O_2,HBr = 507.5$.

CAS — 133099-07-7.

ATC — G04BD10.

ATC Vet — QG04BD10.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p.1219. Darifenacin should be used with caution in patients also receiving inhibitors of cytochrome P450 isoenzymes (see Interactions and Uses and Administration, below). It should also be used with caution in hepatic impairment (see Administration in Hepatic Impairment, below).

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p.1220). Exposure to darifenacin may be increased by drugs that inhibit the cytochrome P450 isoenzymes CYP2D6 and CYP3A4. Inducers of CYP3A4 may reduce plasma concentrations of darifenacin. Dosage adjustment for darifenacin may be necessary (see Uses and Administration, below). Darifenacin itself is also a moderate inhibitor of CYP2D6.

Pharmacokinetics

After an oral dose, darifenacin is subject to extensive first-pass metabolism and has a bioavailability of about 15 to 19%. It is about 98% bound to plasma proteins. Darifenacin is metabolised in the liver by the cytochrome P450 isoenzymes CYP2D6 and CYP3A4. The pharmacokinetics of darifenacin at steady state are dose-dependent because of the saturation of CYP2D6 metabolism. Most of a dose is excreted as metabolites in the urine and faeces.

◊ References.

1. Kerbusch T, *et al.* Population pharmacokinetic modelling of darifenacin and its hydroxylated metabolite using pooled data, incorporating saturable first-pass metabolism, CYP2D6 genotype and formulation-dependent bioavailability. *Br J Clin Pharmacol* 2003; **56:** 639–52.
2. Devineni D, *et al.* Pharmacokinetics of darifenacin, an M selective receptor antagonist: effects of renal or hepatic impairment. *Br J Clin Pharmacol* 2005; **59:** 632–3.
3. Skerjanec A. The clinical pharmacokinetics of darifenacin. *Clin Pharmacokinet* 2006; **45:** 325–50.

Uses and Administration

Darifenacin is a selective M_3 antimuscarinic with actions similar to those of atropine (p.1220); it is claimed to have a greater selectivity for the muscarinic receptors of the bladder.

Darifenacin is used in the management of urinary frequency, urgency, and incontinence in detrusor instability (p.2180). It is given orally as the hydrobromide but doses are described in terms of the base: darifenacin hydrobromide 8.9 mg is equivalent to about 7.5 mg of darifenacin. The usual initial dose is the equivalent of darifenacin 7.5 mg once daily; after 2 weeks of treatment this may be increased to 15 mg once daily if necessary.

The starting dose of 7.5 mg should only be increased with caution in patients also receiving potent inhibitors of the cytochrome P450 isoenzyme CYP2D6, such as paroxetine and terbinafine. Darifenacin should be avoided, or a dose of 7.5 mg daily not exceeded, in patients also receiving potent inhibitors of CYP3A4, such as HIV-protease inhibitors, ketoconazole, and itraconazole. The dose of darifenacin should be increased with caution in the presence of moderate inhibitors of CYP3A4, such as macrolide antibacterials, fluconazole, and grapefruit juice.

Darifenacin should be used with caution in hepatic impairment, see below.

Darifenacin is being studied in irritable bowel syndrome.

◊ References.

1. Haab F, *et al.* Darifenacin, an M selective receptor antagonist, is an effective and well-tolerated once-daily treatment for overactive bladder. *Eur Urol* 2004; **45:** 420–9.
2. Chapple C, *et al.* A pooled analysis of three phase III studies to investigate the efficacy, tolerability and safety of darifenacin, a muscarinic M selective receptor antagonist, in the treatment of overactive bladder. *BJU Int* 2005; **95:** 993–1001.
3. Foote J, *et al.* Treatment of overactive bladder in the older patient: pooled analysis of three phase III studies of darifenacin, an M selective receptor antagonist. *Eur Urol* 2005; **48:** 471–7.
4. Parsons M, *et al.* Darifenacin in the treatment of overactive bladder. *Int J Clin Pract* 2005; **59:** 831–8.

Administration in hepatic impairment. Licensed product information states that the dose of darifenacin should not exceed 7.5 mg once daily in patients with moderate hepatic impairment (Child-Pugh category B), and its use should be avoided in severe impairment (Child-Pugh category C).

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Emselex; ***Ger.:*** Emselex; ***Gr.:*** Emselex; ***Hung.:*** Emselex; ***Neth.:*** Emselex; ***S.Afr.:*** Enablex; ***Swed.:*** Emselex; ***UK:*** Emselex; ***USA:*** Enablex.

Desmopressin *(BAN, rINN)*

DDAVP; Desmopresina; Desmopresinas; Desmopressiini; Desmopressine; Desmopressinum; Dezmopresszin. 1-(3-Mercaptopropionic acid)-8-D-arginine-vasopressin; [1-Deamino,8-D-arginine]vasopressin.

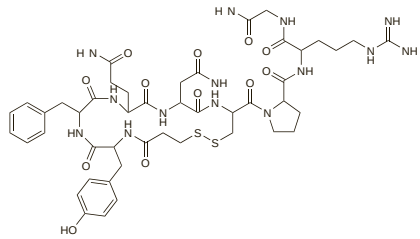
Дезмопрессин

$C_{46}H_{64}N_{14}O_{12}S_2 = 1069.2$.

CAS — 16679-58-6.

ATC — H01BA02.

ATC Vet — QH01BA02.



Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Desmopressin). A synthetic cyclic nonapeptide, available as an acetate. A white or almost white, fluffy powder. Soluble in water, in alcohol, and in glacial acetic acid. Store in airtight containers at 2° to 8°. Protect from light.

Desmopressin Acetate *(BANM, USAN, rINNM)*

Acetato de desmopresina; Desmopresin Asetat; Desmopressine, Acétate de; Desmopressini Acetas.

Дезмопрессина Ацетат

$C_{46}H_{64}N_{14}O_{12}S_2,C_2H_4O_2,3H_2O = 1183.3$.

CAS — 62288-83-9 (anhydrous desmopressin acetate); 62357-86-2 (desmopressin acetate trihydrate).

ATC — H01BA02.

ATC Vet — QH01BA02.

Pharmacopoeias. In *US*.
USP 31 (Desmopressin Acetate). A white, fluffy powder. Soluble in water, in alcohol, and in acetic acid. Store in airtight containers at a temperature not exceeding 25°, but preferably between 2° and 8°. Protect from light.

Units

27 units of desmopressin are contained in about 27 micrograms of desmopressin (with 5 mg of human albumin and citric acid) in one ampoule of the first International Standard (1980).

Adverse Effects and Precautions

Adverse effects of desmopressin include headache, nausea, and mild abdominal cramps; there may be pain and swelling at the site of injection. With large intravenous doses hypotension, with tachycardia and facial flushing, may occur; some patients may experience an increase in blood pressure. Occasionally there may be cerebral or coronary thrombosis. Hypersensitivity reactions have also occurred. The antidiuretic action of desmopressin can produce water intoxication and hyponatraemia, occasionally leading to convulsions. The incidence of hyponatraemia may be higher with nasal formulations than with oral formulations. Nasal doses may cause local irritation, congestion, and epistaxis.

Precautions to be observed with desmopressin are similar to those for vasopressin (see p.2412). It should not be given to patients with type IIB von Willebrand's disease, in whom the release of clotting factors may lead to platelet aggregation and thrombocytopenia. When desmopressin is used diagnostically, or for the treatment of enuresis, the fluid intake should be limited to a minimum and only to satisfy thirst from 1 hour before to 8 hours after use (see also Effects on Electrolytes, below).

Effects on the cardiovascular system. Facial flushing and warmth after intravenous desmopressin reflect a vasodilator action[1] or may be due to an opioid mechanism in the CNS.[2] A drop in diastolic blood pressure of about 14 mmHg and an increase in heart rate of 20 beats/minute are the rule during intravenous infusion of desmopressin in doses of 400 nanograms/kg or more.[1] The hypotensive effects of desmopressin were responsible for a serious reaction, involving cyanosis and dyspnoea, in a 21-month-old child with cyanotic heart disease.[3] Thrombosis (including myocardial infarction)[4-6] and cerebral infarction[7] have been associated rarely with the use of intravenous desmopressin. An analysis[8] of events in patients undergoing major surgery suggested, however, that co-existing conditions in elderly patients and the surgical procedures themselves were associated with a high risk of thrombosis, and that desmopressin did not increase the incidence of thrombotic events.

Licensed product information also warns of the possibility of an increase in blood pressure.

1. Brommer EJP, *et al.* Desmopressin and hypotension. *Ann Intern Med* 1985; **103:** 962.

2. Pigache RM. Facial flushing induced by vasopressin-like peptides lacking pressor activity. *J Clin Pharmacol* 1984; **17:** 369–71.
3. Israels SJ, Kobrinsky NL. Serious reaction to desmopressin in a child with cyanotic heart disease. *N Engl J Med* 1989; **320:** 1563–4.
4. Anonymous. Desmopressin and arterial thrombosis. *Lancet* 1989; **i:** 938–9.
5. Mannucci PM, Lusher JM. Desmopressin and thrombosis. *Lancet* 1989; **ii:** 675–6.
6. Hartmann S, Reinhart W. Fatal complication of desmopressin. *Lancet* 1995; **345:** 1302–3. Correction. *ibid.;* 1648.
7. Grunwald Z, Sather SDC. Intraoperative cerebral infarction after desmopressin administration in infant with end-stage renal disease. *Lancet* 1995; **345:** 1364–5.
8. Mannucci PM, *et al.* Desmopressin, surgery and thrombosis. *Thromb Haemost* 1994; **71:** 154–5.

Effects on electrolytes. There have been a number of reports of seizures due to hyponatraemia and water intoxication after intranasal[1-8] or intravenous[9] desmopressin. The UK CSM noted in March 1996 that it had received reports of hyponatraemic convulsions in 21 children and 3 adults receiving desmopressin (which it somewhat inaccurately described as vasopressin).[10] It was recommended that when this drug was used to treat primary nocturnal enuresis the risks of hyponatraemia should be minimised by

- avoiding concomitant use of drugs, such as *tricyclic antidepressants*, that increase endogenous ADH secretion
- keeping to the recommended starting dose
- avoiding excessive fluid intake, including ingestion of water during swimming
- stopping treatment temporarily if vomiting or diarrhoea occurred, to allow recovery of normal fluid and electrolyte balance

Some have suggested that no more than 240 mL of fluid should be ingested on nights when desmopressin is given.[7] Others have suggested that serum-sodium concentrations be measured 24 to 48 hours, 1 week, and 1 month after starting treatment with desmopressin.[8] A systematic review[11] of the risk in older patients being treated for nocturia, which found the incidence of hyponatraemia to be about 8%, also recommended regular monitoring.

In April 2007, the MHRA requested that the indication for the treatment of primary nocturnal enuresis be removed from desmopressin nasal spray formulations in the UK. Compared with oral formulations, nasal forms were associated with most of the serious adverse effects reported in patients with primary nocturnal enuresis; these included hyponatraemia, water intoxication, and convulsions. Hyponatraemia was reported at a rate of about 15 cases per 100 000 years of patient exposure for nasal dosage forms, compared with 6 cases per 100 000 patient years for oral formulations; hyponatraemia was mainly associated with overdose, excessive fluid intake, or inappropriate use.[12] The FDA has issued similar warnings.[13]

1. Simmonds EJ, *et al.* Convulsions and coma after intranasal desmopressin in cystic fibrosis. *BMJ* 1988; **297:** 1614.
2. Salvatoni A, *et al.* Hyponatremia and seizures during desmopressin acetate treatment in hypothyroidism. *J Pediatr* 1990; **116:** 835–6.
3. Davis RC, *et al.* Nocturnal enuresis. *Lancet* 1992; **340:** 1550.
4. Hamed M, *et al.* Hyponatraemic convulsion associated with desmopressin and imipramine treatment. *BMJ* 1993; **306:** 1169.
5. Hourihane J, Salisbury AJ. Use caution in prescribing desmopressin for nocturnal enuresis. *BMJ* 1993; **306:** 1545.
6. Robson WLM, Leung AKC. Hyponatraemia following desmopressin. *BMJ* 1993; **307:** 64–5.
7. Robson WLM, *et al.* Hyponatremia in patients with nocturnal enuresis treated with DDAVP. *Eur J Pediatr* 1996; **155:** 959–62.
8. Odeh M, Oliven A. Coma and seizures due to severe hyponatremia and water intoxication in an adult with intranasal desmopressin therapy for nocturnal enuresis. *J Clin Pharmacol* 2001; **41:** 582–4.
9. Shepherd LL, *et al.* Hyponatremia and seizures after intravenous administration of desmopressin acetate for surgical hemostasis. *J Pediatr* 1989; **114:** 470–2.
10. Committee on Safety of Medicines/Medicines Control Agency. Hyponatraemic convulsions in patients with enuresis treated with vasopressin. *Current Problems* 1996; **22:** 4.
11. Weatherall M. The risk of hyponatremia in older adults using desmopressin for nocturia: a systematic review and meta-analysis. *Neurourol Urodyn* 2004; **23:** 302–5.
12. Medicines and Healthcare products Regulatory Agency. Desmopressin nasal spray: removal of the primary nocturnal enuresis (bedwetting) indication (issued 18th April 2007). Available at: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON2030795 (accessed 02/09/08)
13. FDA. Information for healthcare professionals: desmopressin acetate (marketed as DDAVP Nasal Spray, DDAVP Rhinal Tube, DDAVP, DDVP, Minirin, and Stimate Nasal Spray) (issued 4th December 2007). Available at: http://www.fda.gov/ cder/drug/InfoSheets/HCP/desmopressinHCP.htm (accessed 11/06/08)

Effects on the eyes. Pseudotumor cerebri associated with desmopressin treatment has been reported in a patient.[1]

1. Neely DE, *et al.* Desmopressin (DDAVP)-induced pseudotumor cerebri. *J Pediatr* 2003; **143:** 808.

Effects on mental function. Paranoid psychosis occurred after desmopressin therapy in a patient with Alzheimer's dementia.[1]

1. Collins GB, *et al.* Paranoid psychosis after DDAVP therapy for Alzheimer's dementia. *Lancet* 1981; **ii:** 808.

Tolerance. In 3 uraemic patients desmopressin infusion produced an initial shortening of the bleeding time but after repeated infusions this response was reduced and there was even some increase in baseline bleeding times.[1] Two infusions of desmopressin 300 nanograms/kg in one day appear to induce a near maximum response; different treatment is required subsequently.

1. Canavese C, *et al.* Reduced response of uraemic bleeding time to repeated doses of desmopressin. *Lancet* 1985; **i:** 867–8.

Interactions

As for Vasopressin, p.2412. See also Effects on Electrolytes, above. NSAIDs, such as ibuprofen (see Effects on Electrolytes under Ibuprofen, p.64) and indometacin, may enhance the antidiuretic effect of desmopressin.

Gastrointestinal drugs. In a study[1] in healthy subjects, *loperamide* caused a threefold increase in the gastrointestinal absorption of oral desmopressin, presumably by slowing gastrointestinal motility. In the same study, however, increased motility caused by *erythromycin* did not affect desmopressin absorption.

1. Callréus T, *et al.* Changes in gastrointestinal motility influence the absorption of desmopressin. *Eur J Clin Pharmacol* 1999; **55:** 305–9.

Pharmacokinetics

Desmopressin is absorbed from the nasal mucosa with a bioavailability of 10 to 20%. After oral doses it is largely destroyed in the gastrointestinal tract but sufficient is absorbed from high doses to produce therapeutic effects. When given intravenously desmopressin exhibits biphasic pharmacokinetics, with half-lives of about 8 minutes and 75 minutes for the 2 phases respectively.

◊ References.

1. Fjellestad-Paulsen A, *et al.* Pharmacokinetics of 1-deamino-8-D-arginine vasopressin after various routes of administration in healthy volunteers. *Clin Endocrinol (Oxf)* 1993; **38:** 177–82.
2. Lam KSL, *et al.* Pharmacokinetics, pharmacodynamics, long-term efficacy and safety of oral 1-deamino-8- -arginine vasopressin in adult patients with central diabetes insipidus. *Br J Clin Pharmacol* 1996; **42:** 379–85.
3. Agersø H, *et al.* Pharmacokinetics and renal excretion of desmopressin after intravenous administration to healthy subjects and renally impaired patients. *Br J Clin Pharmacol* 2004; **58:** 352–8.
4. Østerberg O, *et al.* Pharmacokinetics of desmopressin administrated [sic] as an oral lyophilisate dosage form in children with primary nocturnal enuresis and healthy adults. *J Clin Pharmacol* 2006; **46:** 1204–11.

Uses and Administration

Desmopressin is a synthetic analogue of vasopressin (p.2411). It has greater antidiuretic activity and a more prolonged action than vasopressin or lypressin. It also stimulates factor VIII and plasminogen activator activity in the blood, but has little pressor activity.

Desmopressin is used in the diagnosis and treatment of cranial diabetes insipidus, in the treatment of nocturnal enuresis, and in tests of renal function. It is also used in the management of mild or moderate haemophilia and type I von Willebrand's disease, and in tests of fibrinolytic response.

It is given as the acetate, orally, as a solution intranasally, and by injection. The intranasal dose is about ten times that required intravenously and the oral dose about ten times greater than the intranasal dose. Doses are usually expressed in terms of desmopressin acetate, but for some preparations they are given in terms of the base; 110.7 micrograms of desmopressin acetate is equivalent to about 100 micrograms of desmopressin.

In the control of **cranial diabetes insipidus**, desmopressin acetate is given orally in usual initial doses of 100 micrograms three times daily. Doses may be adjusted according to response, with maintenance doses usually between 100 and 200 micrograms three times daily though total doses of between 100 micrograms and 1200 micrograms daily have been used.

A sublingual lyophilisate preparation containing desmopressin acetate is also available in the UK, but doses are expressed in terms of the base. The initial dose is equivalent to 60 micrograms of desmopressin given sublingually three times daily. The dose may be adjusted, with usual maintenance doses between 60 and 120 micrograms three times daily, though total doses of up to 720 micrograms daily have been used.

Desmopressin acetate may also be used intranasally in usual doses of 10 to 40 micrograms daily as a single dose or in divided doses.

It may also be given subcutaneously, intramuscularly, or intravenously in a dose of 1 to 4 micrograms daily.

A single intranasal dose of 20 micrograms or 2 micrograms subcutaneously or intramuscularly has been given in the **diagnosis** of diabetes insipidus.

In the **testing of renal function**, desmopressin acetate has been given intranasally in single doses of 40 micrograms and subcutaneously or intramuscularly in doses of 2 micrograms.

In the management of **primary nocturnal enuresis**, desmopressin acetate is given in usual oral doses of 200 to 400 micrograms. The sublingual lyophilisate preparation may be given in a dose equivalent to desmopressin 120 micrograms at bedtime, increasing to 240 micrograms if needed. The need for continued treatment should be reassessed after 3 months by withdrawing desmopressin for at least 1 week. For the view that nasal preparations should not be used for primary nocturnal enuresis, see Effects on Electrolytes, under Adverse Effects, above. For the control of **nocturia** in multiple sclerosis desmopressin acetate 10 to 20 micrograms intranasally at bedtime is recommended (but see Urinary Incontinence, below).

Desmopressin acetate is given by intravenous infusion to boost concentrations of factor VIII before surgical procedures in patients with mild to moderate **haemophilia** or **type I von Willebrand's disease**. The usual dose is 300 or 400 nanograms/kg by slow intravenous infusion over 15 to 30 minutes just before surgery. It may be used similarly to treat spontaneous or trauma-induced bleeding episodes in these patients. It is also given intranasally in doses of 150 micrograms (in patients weighing less than 50 kg) or 300 micrograms; it should be given within 2 hours before surgery.

For **testing of fibrinolytic response** desmopressin acetate may be given by intravenous infusion in doses of 400 nanograms/kg over 20 minutes; a sample of venous blood is taken 20 minutes after completing the infusion and tested for fibrinolytic activity on fibrin plates. Alternatively, a dose of 300 micrograms may be given intranasally 60 minutes before collecting the blood sample.

For details of uses and doses in children, see below.

Administration in children. Although some desmopressin preparations are licensed in the UK and the USA for paediatric use, the indications are generally fewer than for adults and the age ranges are often not specified.

The *BNFC*, however, lists doses for both licensed and unlicensed indications, and the full range of *BNFC* doses, given according to age, is as follows:

Treatment of diabetes insipidus

orally

- neonate: initially 1 to 4 micrograms 2 or 3 times daily, adjusted according to response
- 1 month to 2 years: initially 10 micrograms 2 or 3 times daily, adjusted according to response (range 30 to 150 micrograms daily)
- 2 to 12 years: initially 50 micrograms 2 or 3 times daily, adjusted according to response (range 100 to 800 micrograms daily)
- 12 to 18 years: initially 100 micrograms 2 or 3 times daily, adjusted according to response (range 200 to 1200 micrograms daily)

sublingually

- 2 to 18 years: initially 60 micrograms 3 times daily, adjusted according to response (range 40 to 240 micrograms 3 times daily)

intranasally

- neonate: initially 100 to 500 nanograms, adjusted according to response (range 1.25 to 10 micrograms daily as a single dose or in 2 divided doses)
- 1 month to 2 years: initially 2.5 to 5 micrograms once or twice daily, adjusted according to response
- 2 to 12 years: initially 5 to 20 micrograms once or twice daily, adjusted according to response
- 12 to 18 years: initially 10 to 20 micrograms once or twice daily, adjusted according to response

subcutaneously or *intramuscularly*

- neonate: initially 100 nanograms once daily, adjusted according to response (use the intramuscular route only)

- 1 month to 12 years: initially 400 nanograms once daily, adjusted according to response
- 12 to 18 years: initially 1 to 4 micrograms once daily, adjusted according to response

Test for suspected diabetes insipidus

intranasally

- 1 month to 2 years: 5 to 10 micrograms as a single dose (although this test is not usually recommended in young children)
- 2 to 12 years: 10 to 20 micrograms as a single dose
- 12 to 18 years: 20 micrograms as a single dose

subcutaneously or *intramuscularly*

- 1 month to 2 years: 400 nanograms as a single dose (although this test is not usually recommended in young children)
- 2 to 12 years: 0.5 to 1 microgram as a single dose
- 12 to 18 years: 1 to 2 micrograms as a single dose

Testing of renal function

intranasally

- 1 month to 1 year: 10 micrograms
- 1 to 15 years: 20 micrograms
- 15 to 18 years: 40 micrograms

subcutaneously or *intramuscularly*

- 1 month to 1 year: 400 nanograms
- 1 to 18 years: 2 micrograms

Primary nocturnal enuresis

orally

- 5 to 18 years (but preferably over 7 years): 200 micrograms at bedtime, increased if necessary to 400 micrograms

sublingually

- 5 to 18 years (but preferably over 7 years): 120 micrograms at bedtime, increased if necessary to 240 micrograms

The need for continued treatment with either route should be reassessed after 3 months by withdrawing desmopressin for at least 1 week

Mild to moderate **haemophilia** or **von Willebrand's disease**

intravenously (infusion over 20 minutes) or *subcutaneously*

- 1 month to 18 years: 300 nanograms/kg as a single dose immediately before surgery or after trauma; the dose may be repeated at intervals of 12 hours if no tachycardia occurs

intranasally

- 1 to 18 years: 4 micrograms/kg as a single dose; for preoperative use give 2 hours before the procedure

Testing of fibrinolytic response

intravenously (infusion over 20 minutes) or *subcutaneously*

- 2 to 18 years: 300 nanograms/kg as a single dose; blood is sampled after 20 minutes for fibrinolytic activity

Diabetes insipidus. Desmopressin is the usual treatment for cranial diabetes insipidus (p.2179).

Haemorrhagic disorders. Desmopressin is used in the management of patients with mild haemophilia A, carriers of haemophilia with low factor VIII concentrations, and patients with acquired haemophilia who have low titres of antibodies to factor VIII (see Haemophilias, p.1048). Desmopressin is also used in von Willebrand's disease (p.1051). The use of desmopressin results in a two- to sixfold increase in plasma concentrations of factor VIII and von Willebrand factor,[1] and patients must have measurable baseline concentrations of these factors in order to respond to desmopressin.[1,2] In general, a baseline factor VIII concentration of 0.1 to 0.15 units/mL is needed to achieve post-injection concentrations of about 0.3 to 0.5 units/mL, which are generally sufficient for minor bleeding or lesser procedures. Concentrations of at least 0.7 to 1 unit/mL must be achieved for major surgery.[1] Desmopressin can be given subcutaneously, but the peak levels of factor VIII are reached later than after intravenous use. Intranasal use is also effective and allows patients to treat bleeding episodes themselves, without delay, outside hospital.[1] The use of desmopressin as an alternative to blood products has been recommended whenever possible in the treatment of these disorders, as a precaution against blood-borne infection.[1]

Bleeding due to liver disease has been controlled by desmopressin,[3,4] as has that associated with uraemia[5-8] (but for a report of tolerance to the effects of repeated doses of desmopressin in uraemic patients, see under Adverse Effects and Precautions, above), and there are reports of bleeding being controlled in other disorders such as telangiectasia[9] and platelet storage deficiency.[10-12] See also Haemorrhagic Disorders in Vasopressin (p.2412), and Variceal Haemorrhage in Vasopressin (p.2413) and Terlipressin (p.2396).

Desmopressin has been tried in surgical procedures with conflicting results.[2] A meta-analysis, which mainly included trials in cardiac surgery, found no evidence that desmopressin reduces perioperative blood transfusion in patients who do not have congenital bleeding disorders.[13] A possible role for desmopressin has been proposed in the control of surgical bleeding in patients whose religious beliefs preclude the use of blood products.[14,15] It has also been reported to be effective in postoperative aspirin-related bleeding that was previously unresponsive to clotting factors.[16] However, studies of prophylactic desmopressin given to patients who had received aspirin in the 7 days before cardiac bypass surgery have produced conflicting results, with desmopressin either reducing blood loss[17] or having no effect.[18]

1. Lethagen S. Desmopressin in mild hemophilia A: indications, limitations, efficacy, and safety. *Semin Thromb Hemost* 2003; **29:** 101–5.
2. Mannucci PM. Desmopressin (DDAVP) in the treatment of bleeding disorders: the first 20 years. *Blood* 1997; **90:** 2515–21.
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10. Nieuwenhuis HK, Sixma JJ. 1-Desamino-8- -arginine vasopressin (desmopressin) shortens the bleeding time in storage pool deficiency. *Ann Intern Med* 1988; **108:** 65–7.
11. Castaman G, Rodeghiero F. Consistency of responses to separate desmopressin infusions in patients with storage pool disease and isolated prolonged bleeding time. *Thromb Res* 1993; **69:** 407–12.
12. Zatik J, *et al.* Variable response of Hermansky-Pudlak syndrome to prophylactic administration of 1-desamino 8 -arginine in subsequent pregnancies. *Eur J Obstet Gynecol Reprod Biol* 2002; **104:** 165–6.
13. Carless PA, *et al.* Desmopressin for minimising perioperative allogeneic blood transfusion. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 15/09/05).
14. Martens PR. Desmopressin and Jehovah's witness. *Lancet* 1989; **i:** 1322.
15. Beholz S, *et al.* Use of desmopressin and erythropoietin in an anaemic Jehovah's Witness patient with severely impaired coagulation capacity undergoing stentless aortic valve replacement. *Perfusion* 2001; **16:** 485–9.
16. Chard RB, *et al.* Use of desmopressin in the management of aspirin-related and intractable haemorrhage after cardiopulmonary bypass. *Aust N Z J Surg* 1990; **60:** 125–8.
17. Sheridan DP, *et al.* Use of desmopressin acetate to reduce blood transfusion requirements during cardiac surgery in patients with acetylsalicylic-acid-induced platelet dysfunction. *Can J Surg* 1994; **37:** 33–6.
18. Pleym H, *et al.* Prophylactic treatment with desmopressin does not reduce postoperative bleeding after coronary surgery in patients treated with aspirin before surgery. *Anesth Analg* 2004; **98:** 578–84.

Nocturnal enuresis. Desmopressin is one of the main drugs used as an alternative or adjunct to nonpharmacological methods for the treatment of nocturnal enuresis in children (p.2180). Secretion of vasopressin during the night in normal individuals reduces urine output and it has been suggested that nocturnal enuresis in some children might be due to impaired nocturnal secretion of vasopressin. However, other possible mechanisms include bladder instability and reduced nightly functional bladder capacity, and it has been proposed that treatment should be based on a greater consideration of nocturnal enuresis as a multifactorial condition.[1]

The synthetic vasopressin analogue desmopressin is used for its presumed antidiuretic effect on the kidney,[2] although there is some evidence that it may act by some other mechanism, possibly having a central effect.[3,4] It has been shown that desmopressin given at night can be effective in the short-term control of nocturnal enuresis[2,5] and many now consider it to be the drug of choice in terms of safety. There is some evidence[6,7] that long-term use of desmopressin is also effective. However, a meta-analysis suggested that benefit might not be sustained once the drug was stopped.[8] It should not be given when enuresis is due to polydipsia as desmopressin may provoke water intoxication and convulsions due to hyponatraemia. For precautions to be observed when desmopressin is used to treat enuresis, and the view that nasal formulations should not be used for this indication, see Effects on Electrolytes, above.

1. Butler RJ, *et al.* Investigating the three systems approach to complex childhood nocturnal enuresis. *Scand J Urol Nephrol* 2004; **38:** 117–21.
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6. Hjälmås K, *et al.* Long-term treatment with desmopressin in children with primary monosymptomatic nocturnal enuresis: an open multicentre study. *Br J Urol* 1998; **82:** 704–9.
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8. Glazener CMA, Evans JHC. Desmopressin for nocturnal enuresis in children. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 15/09/05).

Orthostatic hypotension. The first drug tried in patients with orthostatic hypotension (p.1530) who cannot be managed by nonpharmacological methods is usually fludrocortisone, but desmopressin is sometimes useful in patients with central neurological abnormalities.[1]

1. Mathias CJ, *et al.* The effect of desmopressin on nocturnal polyuria, overnight weight loss, and morning postural hypotension in patients with autonomic failure. *BMJ* 1986; **293:** 353–4.

Post-dural puncture headache. Desmopressin acetate has been given to adults in a dose of 4 micrograms subcutaneously or intramuscularly for the treatment or prophylaxis of headache due to lumbar puncture, repeated if necessary after 24 hours. However, results have generally been disappointing and many patients respond to conservative treatment (see p.1851).

References.

1. Durward WF, Harrington H. Headache after lumbar puncture. *Lancet* 1976; **ii:** 1403–4.
2. Widerlöv E, Lindström L. DDAVP and headache after lumbar puncture. *Lancet* 1979; **i:** 548.
3. Hansen PE, Hansen JH. DDAVP, a synthetic analogue of vasopressin, in prevention of headache after lumbar puncture and lumbar pneumoencephalography. *Acta Neurol Scand* 1979; **60:** 183–8.
4. Cowan JMA, *et al.* DDAVP in the prevention of headache after lumbar puncture. *BMJ* 1980; **280:** 224.

Renal colic. Intranasal desmopressin is being studied[1] in the management of the pain of acute renal colic (p.5).

1. Zabihi N, Teichman JMH. Dealing with the pain of renal colic. *Lancet* 2001; **358:** 437–8.

Urinary incontinence. Desmopressin given intranasally appeared to be effective in reducing voiding frequency/incontinence when studied in 26 patients with multiple sclerosis whose bladder dysfunction had previously been unresponsive to antimuscarinics;[1] similar results have been reported in other small studies in patients with multiple sclerosis.[2] However, a review of studies using desmopressin to treat nocturia in such patients cast doubt on the clinical relevance of the limited reductions achieved in voiding frequency.[3] Nevertheless, beneficial long-term use of desmopressin for nocturia has been described, with some patients also using it intermittently during the daytime to control symptoms for special occasions.[4] Oral desmopressin has been reported to have a favourable effect on measures such as the number of nocturnal voids and duration of sleep until the first nocturnal void in women[5] and men[6] with nocturia. Beneficial effects were maintained or improved in many responders who were treated for a further 10 or 12 months.[7] In the management of daytime urinary incontinence in women, an improvement in the incidence of periods without leakage during the 4 hours after an intranasal dose of desmopressin has been reported.[8]

For the usual treatment of incontinence, see Urinary Incontinence and Retention, p.2180.

1. Fredrikson S. Nasal spray desmopressin treatment of bladder dysfunction in patients with multiple sclerosis. *Acta Neurol Scand* 1996; **94:** 31–4.
2. Cvetković RS, Plosker GL. Desmopressin: in adults with nocturia. *Drugs* 2005; **65:** 99–107.
3. Ferreira E, Letwin SR. Desmopressin for nocturia and enuresis associated with multiple sclerosis. *Ann Pharmacother* 1998; **32:** 114–16.
4. Tubridy N, *et al.* Long term use of desmopressin for urinary symptoms in multiple sclerosis. *Multiple Sclerosis* 1999; **5:** 416–17.
5. Lose G, *et al.* Efficacy of desmopressin (Minirin) in the treatment of nocturia: a double-blind placebo-controlled study in women. *Am J Obstet Gynecol* 2003; **189:** 1106–13.
6. Mattiasson A, *et al.* Efficacy of desmopressin in the treatment of nocturia: a double-blind placebo-controlled study in men. *BJU Int* 2002; **89:** 855–62.
7. Lose G, *et al.* Clinical experiences with desmopressin for long-term treatment of nocturia. *J Urol (Baltimore)* 2004; **172:** 1021–5.
8. Robinson D, *et al.* Antidiuresis: a new concept in managing female daytime urinary incontinence. *BJU Int* 2004; **93:** 996–1000.

Preparations

BP 2008: Desmopressin Injection; Desmopressin Intranasal Solution; ***USP 31:*** Desmopressin Acetate Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Emosint; Octostim; Presinex; ***Austral.:*** Minirin; Octostim; ***Austria:*** Minirin; Nocturin; Nocutil; Nordurine; Novidin; Octostim; ***Belg.:*** Minirin; ***Braz.:*** Octostim†; ***Canad.:*** DDAVP; Minirin; Octostim; ***Chile:*** DDAVP; Octostim; ***Cz.:*** Adiuretin†; Desmospray; Desmotabs; Minirin; Nocutil†; ***Denm.:*** Minirin; Octostim; ***Fin.:*** Minirin; Octostim; ***Fr.:*** Minirin; Minirinmelt; Octim; ***Ger.:*** Desmogalen; Minirin; Nocutil; Octostim; ***Gr.:*** DDAVP; Defirin; Desmoprol; Esmon; Minirin; ***Hong Kong:*** Minirin; Octostim; ***Hung.:*** Desmopress; Minirin; Nocutil; Octostim; ***India:*** D-Void; ***Irl.:*** DDAVP; Desmospray; Desmotabs; Nordurine; ***Israel:*** Adin; Minirin; Octostim; Presinex; ***Ital.:*** Emosint; Minirin/DDAVP; ***Malaysia:*** Minirin; ***Mex.:*** DDAVP†; Minirin; Nafiset; Octostim; ***Neth.:*** Adiuretin; Minrin; Minurin; Octostim; ***Norw.:*** Minirin; Octostim; ***NZ:*** Minirin; Octostim; ***Philipp.:*** Minirin; ***Pol.:*** Minirin; ***Port.:*** DDAVP; Desmospray; Minirin; ***Rus.:*** Emosint (Эмосинт); Miniрin (Минирин); ***S.Afr.:*** DDAVP; ***Singapore:*** Minirin; Octostim†; ***Spain:*** Minurin; Nocturin; Octostim; Presinex; ***Swed.:*** Minirin; Octostim; ***Switz.:*** Minirin; Nocutil; Octostim; ***Thai.:*** Minirin; ***Turk.:*** Minirin; Octostim; ***UK:*** DDAVP; DesmoMelt; Desmospray; Desmotabs; Nocutil†; Octim; Presinex; ***USA:*** DDAVP; Minirin; Stimate.

Dutasteride *(BAN, USAN, rINN)* ⊗

Dutasterid; Dutasterida; Dutastéride; Dutasteridum; GG-745; GI-198745; GI-198745X. α,α,α,α′,α′,α′-Hexafluoro-3-oxo-4-aza-5α-androst-1-ene-17β-carboxy-2′,5′-xylidide; 3-Oxo-2′,5′-bis-(trifluoromethyl)-4-aza-5α-androst-1-ene-17β-carboxanilide.

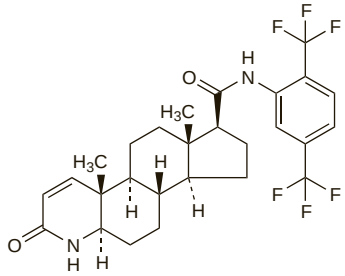
Дутастерид

$C_{27}H_{30}F_6N_2O_2$ = 528.5.

CAS — 164656-23-9.

ATC — G04CB02.

ATC Vet — QG04CB02.



Adverse Effects and Precautions

As for Finasteride, p.2188.

Pharmacokinetics

Dutasteride is absorbed from the gastrointestinal tract, reaching a peak serum concentration in 1 to 3 hours, with a bioavailability of about 60%. It is highly bound to plasma proteins. Dutasteride is metabolised by the cytochrome P450 isoenzymes CYP3A4 and CYP3A5, and most of a dose is excreted as metabolites in the faeces. At steady state the elimination half-life is about 3 to 5 weeks.

Uses and Administration

Dutasteride, like finasteride (p.2189), is an inhibitor of 5α-reductase. Unlike finasteride, it is claimed to inhibit both the type-1 and type-2 isoforms of the enzyme. Dutasteride is used in the treatment of benign prostatic hyperplasia (p.2178); it may reduce the incidence of acute urinary retention and the need for surgery. Dutasteride is given in doses of 500 micrograms daily by mouth. Response may be delayed and treatment for 6 months may be required to assess whether benefit has been achieved.

Dutasteride is under investigation for the prevention of prostate cancer, and has been investigated in the treatment of alopecia.

◊ References.

1. Djavan B, *et al.* Dutasteride: a novel dual inhibitor of 5alpha-reductase for benign prostatic hyperplasia. *Expert Opin Pharmacother* 2005; **6:** 311–17. Correction. *ibid.*; 681.
2. Dolder CR. Dutasteride: a dual 5-α reductase inhibitor for the treatment of symptomatic benign prostatic hyperplasia. *Ann Pharmacother* 2006; **40:** 658–64.
3. Keam SJ, Scott LJ. Dutasteride: a review of its use in the management of prostate disorders. *Drugs* 2008; **68:** 463–85.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Avodart; ***Austria:*** Avodart; Avolve; Zyfetor; ***Belg.:*** Avodart; ***Canad.:*** Avodart; ***Chile:*** Avodart; ***Cz.:*** Avodart; ***Denm.:*** Avodart; ***Fin.:*** Avodart; ***Fr.:*** Avodart; ***Ger.:*** Avodart; ***Gr.:*** Avodart; Duagen; ***India:*** Duprost; ***Indon.:*** Avodart; ***Irl.:*** Avodart; ***Israel:*** Avodart; ***Ital.:*** Avodart; ***Malaysia:*** Avodart; ***Mex.:*** Avodart; ***Neth.:*** Avodart; Duagen; ***Norw.:*** Avodart; ***Philipp.:*** Avodart; ***Pol.:*** Avodart; ***Port.:*** Avodart; Avolve; Duagen; ***Rus.:*** Avodart (Аводарт); ***S.Afr.:*** Avodart; ***Singapore:*** Avodart; ***Spain:*** Avidart; Duagen; ***Swed.:*** Avodart; ***Switz.:*** Avodart; ***Turk.:*** Avodart; ***UK:*** Avodart; ***USA:*** Avodart.

Emepronium Bromide *(BAN, rINN)*

Bromuro de emepronio; Emepronii Bromidum; Émépronium, Bromure d'; Emeproniumbromid; Emeproniumbromidi. Ethyldimethyl(1-methyl-3,3-diphenylpropyl)ammonium bromide.

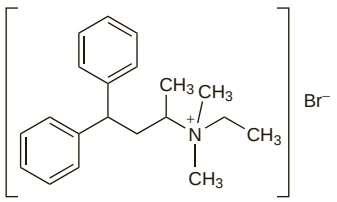
Эмепрония Бромид

$C_{20}H_{28}BrN$ = 362.3.

CAS — 27892-33-7 (emepronium); 3614-30-0 (emepronium bromide).

ATC — G04BD01.

ATC Vet — QG04BD01.



Emepronium Carrageenate *(BAN)*

Emepronio, carragenato de.

ATC — G04BD01.

ATC Vet — QG04BD01.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p.1219.

To avoid oesophageal ulceration, tablets of emepronium bromide should always be swallowed with an adequate volume of water, and patients should always be in the sitting or standing position while, and for 10 to 15 minutes after, taking the tablets. Emepronium is contra-indicated in patients with symptoms or signs of oesophageal obstruction or with pre-existing oesophagitis.

Buccal and oesophageal ulceration. Tablet-induced oesophageal damage is a widely recognised problem and is related to direct mucosal injury by the medication. Emepronium bromide has been frequently implicated in this type of mucosal injury, although it rarely results in stricture formation.[1]

1. McCord GS, Clouse RE. Pill-induced esophageal strictures: clinical features and risk factors for development. *Am J Med* 1990; **88:** 512–18.

Interactions

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

Pharmacokinetics

Emepronium is incompletely absorbed from the gastrointestinal tract and is mainly excreted unchanged in the urine and faeces. It does not readily cross the blood-brain barrier at therapeutic doses.

Uses and Administration

Emepronium is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p.1220). It has been used orally as the bromide and the carrageenate in the treatment of urinary frequency and incontinence (p.2180); the bromide has also been given by subcutaneous or intramuscular injection.

Urinary incontinence. In the UK, guidelines issued by NICE suggest that emepronium should not be recommended for the treatment of urinary incontinence or overactive bladder in women; other antimuscarinics are preferred.[1]

1. NICE. Urinary incontinence: the management of urinary incontinence in women (issued October 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/CG40NICEguideline.pdf (accessed 02/09/08)

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Cetiprin†; ***Braz.:*** Cetiprin†; ***Denm.:*** Cetiprin†; ***Fin.:*** Cetiprin Novum†; ***Neth.:*** Cetiprin†; ***Norw.:*** Cetiprin†; ***Swed.:*** Cetiprin†.

Fesoterodine *(rINN)*

Fesoterodina; Fésotérodine; Fesoterodinum. 2-[(1*R*)-3-(Diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenyl isobutyrate.

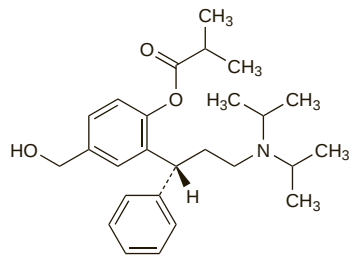
Фезотеродин

$C_{26}H_{37}NO_3$ = 411.6.

CAS — 286930-02-7.

ATC — G04BD11.

ATC Vet — QG04BD11.



Fesoterodine Fumarate *(USAN, rINNM)*

Fésotérodine, Fumarate de; Fesoterodini Fumaras; Fumarato de fesoterodina; SPM-907; SPM-8272.

Фезотеродина Фумарат

$C_{26}H_{37}NO_3.C_4H_4O_4$ = 527.6.

CAS — 286930-03-8.

Profile

Fesoterodine is a selective M_3 antimuscarinic used in the management of urinary frequency, urgency, and incontinence in overactive bladder syndrome (p.2180). It is given orally as the fumarate; the usual initial dose is 4 mg once daily, increased to a maximum of 8 mg once daily if necessary, according to response. Patients should be re-evaluated after 8 weeks of treatment. The dose of fesoterodine fumarate should not exceed 4 mg once daily in patients receiving potent CYP3A4 or CYP2D6 inhibitors. For doses in hepatic and renal impairment, see below.

Administration in hepatic impairment. UK licensed product information for fesoterodine fumarate states that patients with mild hepatic impairment should increase their dose with caution; those also receiving moderate CYP3A4 inhibitors should not exceed a dose of fesoterodine fumarate 4 mg once daily, and concomitant potent CYP3A4 inhibitors are not recommended. Patients with moderate impairment should not exceed a dose of 4 mg once daily and concomitant moderate or potent CYP3A4 inhibitors are not recommended. Fesoterodine fumarate is contra-indicated in those with severe impairment.

Administration in renal impairment. UK licensed product information for fesoterodine fumarate states that patients with mild (GFR 50 to 80 mL/minute) or moderate (GFR 30 to 50 mL/minute) renal impairment, should increase their dose with caution; those also receiving moderate CYP3A4 inhibitors should not exceed a dose of fesoterodine fumarate 4 mg once daily, and concomitant potent CYP3A4 inhibitors are not recommended. Patients with severe impairment (GFR less than 30 mL/minute) should not exceed a dose of 4 mg once daily and concomitant moderate or potent CYP3A4 inhibitors are not recommended.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Toviaz; ***Port.:*** Toviaz; ***UK:*** Toviaz.

Finasteride *(BAN, USAN, rINN)* ⊗

Finasterid; Finasterida; Finasteridas; Finastéride; Finasteridi; Finasteridum; Finaszterid; MK-906; MK-0906; YM-152. *N-tert*-Butyl-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide.

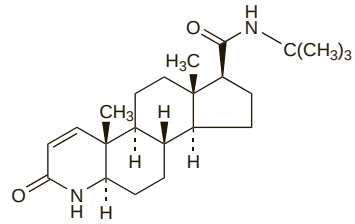
Финастерид

$C_{23}H_{36}N_2O_2$ = 372.5.

CAS — 98319-26-7.

ATC — D11AX10; G04CB01.

ATC Vet — QD11AX10; QG04CB01.



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

Ph. Eur. 6.2 (Finasteride). A white or almost white crystalline powder. It exhibits polymorphism. Practically insoluble in water; freely soluble in dehydrated alcohol and in dichloromethane. Protect from light.

USP 31 (Finasteride). A white to off-white crystalline solid. Very slightly soluble in water; freely soluble in alcohol and in chloroform. Store in airtight containers.

Adverse Effects

The most commonly reported adverse effects of finasteride are decreased libido, erectile dysfunction, ejaculation disorders, and reduced volume of ejaculate.

Breast tenderness and enlargement (gynaecomastia) may occur, and there have been reports of hypersensitivity reactions such as swelling of the lips and face, pruritus, urticaria, and rashes. Testicular pain has also been reported.

Incidence of adverse effects. In a study using prescription event monitoring data,[1] the most commonly reported adverse effects of finasteride in 14 772 patients were impotence or ejaculatory failure (2.1% of patients), reduced libido (1%), and breast disorders such as gynaecomastia (0.4%). Adverse effects reported in a single patient each, and verified on rechallenge, were exfoliative dermatitis, perioral numbness, and swollen glands. Finasteride appeared to be associated with ataxia in 1 patient and wheeziness in another.

1. Wilton L, *et al.* The safety of finasteride used in benign prostatic hypertrophy: a non-interventional observational cohort study in 14 772 patients. *Br J Urol* 1996; **78:** 379–84.

Effects on the breast. Gynaecomastia was the adverse effect of finasteride most frequently reported to the FDA between June 1992 and February 1995 (a total of 214 reports).[1] The onset after therapy ranged from 14 days to 2.5 years, and the condition could be unilateral or bilateral. Mastectomy was performed in 12 men. Of the 86 men for whom follow-up information was available, partial or complete remission of gynaecomastia occurred in 80%, and no change occurred in 20%. In 2 of the cases, primary intraductal breast carcinoma was subsequently found, although 1