**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.

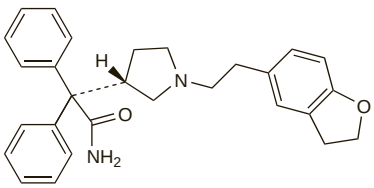
Дарифенацин

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

*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.

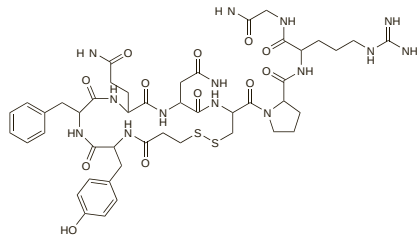
Дезмопрессин

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

*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.