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

Pharmacokinetics
After oral doses of trospium chloride, peak plasma concentrations are reached at 4 to 6 hours. The bioavailability of trospium chloride is reduced by the simultaneous intake of food, especially with a high fat content. Plasma protein binding ranges from about 50% to about 80%. Trospium is excreted in the urine mainly by active renal tubular secretion as unchanged drug; about 10% appears as the spiroalcohol metabolite. The plasma half-life has been reported to be between 10 and 20 hours for the immediate-release preparation, and about 35 hours for the modified-release preparation. The mean half-life has been reported to be prolonged twofold in patients with severe renal impairment (creatinine clearance between 8 and 32 mL/minute). Trospium has been reported to cross the placenta and has been detected in the milk of *rats*.

◊ Reviews.

1. Doroshyenko O, *et al.* Clinical pharmacokinetics of trospium chloride. *Clin Pharmacokinet* 2005; **44:** 701–20.

◊ For reference to the bioavailability of trospium chloride after intravesical instillation, see below.

Uses and Administration
Trospium chloride is a quaternary ammonium antimuscarinic with actions similar to those of atropine (p.1220). It is used for the management of urinary frequency, urgency, and incontinence in detrusor instability or detrusor hyperreflexia. It has also been used as an antispasmodic.

The immediate-release preparation is given orally in usual doses of 20 mg twice daily before meals on an empty stomach. Lower doses of 20 mg once daily may be warranted in patients aged 75 years and over. The need for continued treatment should be assessed at regular intervals of 3 to 6 months. A modified-release preparation is also available in some countries; the usual oral dose is 60 mg once daily in the morning, at least one hour before food. For use in patients with hepatic or renal impairment, see below.

Trospium chloride has also been given by slow intravenous injection. An inhaled formulation of trospium chloride for the treatment of chronic obstructive pulmonary disease is also being developed.

◊ References.

1. Walter P, *et al.* Bioavailability of trospium chloride after intravesical instillation in patients with neurogenic lower urinary tract dysfunction: a pilot study. *Neurourol Urodyn* 1999; **18:** 447–53.
2. Frohlich G, *et al.* Trospium chloride in patients with detrusor overactivity: meta-analysis of placebo-controlled, randomized, double-blind, multi-center clinical trials on the efficacy and safety of 20 mg trospium chloride twice daily. *Int J Clin Pharmacol Ther* 2002; **40:** 295–303.
3. Halaska M, *et al.* Controlled, double-blind, multicentre clinical trial to investigate long-term tolerability and efficacy of trospium chloride in patients with detrusor instability. *World J Urol* 2003; **20:** 392–9.
4. Lopez Pereira P, *et al.* Trospium chloride for the treatment of detrusor instability in children. *J Urol (Baltimore)* 2003; **170:** 1978–81.
5. Zinner N, *et al.* Trospium chloride improves overactive bladder symptoms: a multicenter phase III trial. *J Urol (Baltimore)* 2004; **171:** 2311–15.
6. Rovner ES. Trospium chloride in the management of overactive bladder. *Drugs* 2004; **64:** 2433–46.
7. Singh-Franco D, *et al.* Trospium chloride for the treatment of overactive bladder with urge incontinence. *Clin Ther* 2005; **27:** 511–30.
8. Rudy D, *et al.* Multicenter phase III trial studying trospium chloride in patients with overactive bladder. *Urology* 2006; **67:** 275–80.
9. Menarini M, *et al.* TcP128-Study Group. Trospium chloride in patients with neurogenic detrusor overactivity: is dose titration of benefit to the patients? *Int J Clin Pharmacol Ther* 2006; **44:** 623–32.
10. Staskin D, *et al.* Trospium Study Group. Once daily trospium chloride is effective and well tolerated for the treatment of overactive bladder: results from a multicenter phase III trial. *J Urol (Baltimore)* 2007; **178:** 978–83.

Administration in hepatic impairment. Licensed product information for trospium chloride states that maximum plasma concentrations and area under the concentration-time curve were increased in patients with mild (Child-Pugh score 5 to 6) or moderate (Child-Pugh score 7 to 12) hepatic impairment compared with healthy subjects. There is no information regarding the use of trospium chloride in patients with severe hepatic impairment. UK licensed product information advises caution in those with mild to moderate impairment, and advises against treatment in severe hepatic impairment. US licensed product information for both the immediate-release and the modified-release preparations advises caution in those with moderate to severe hepatic impairment. No specific dosage recommendations are given in either the UK or US product information.

Administration in renal impairment. Trospium chloride is mainly eliminated through active tubular secretion. Licensed product information states that increases in maximum plasma concentrations, area under the concentration-time curve, and half-life have been seen in patients with severe renal impairment given the immediate-release preparation; the pharmacokinetics of trospium chloride have not been studied in those with mild or moderate renal impairment.

UK licensed product information for the immediate-release preparation advises caution in those with mild to moderate renal impairment, while allowing for an oral dose of trospium chloride 20 mg once daily, or every alternate day, in those with severe renal impairment, defined as creatinine clearance (CC) of between 10 and 30 mL/minute per 1.73m^2.

US licensed product information for the immediate-release preparation recommends a dose of 20 mg daily at bedtime for those with severe renal impairment (defined as CC less than 30 mL/minute). The modified-release preparation is not recommended for use in patients with severe renal impairment.

Preparations
Proprietary Preparations (details are given in Part 3)

Arg.: Spasmex; ***Austria:*** Inkontan; Rekont; Spasmolyt; ***Chile:*** Spasmex; ***Cz.:*** Spasmed; Spasmex; Uraplex; ***Denm.:*** Spasmo-Lyt; ***Fin.:*** Spasmo-Lyt; ***Fr.:*** Ceris; ***Ger.:*** Spasmex; Spasmo-Rhoival TC; Spasmo-Urgenin TC; Spasmolyt; Trospi; ***Gr.:*** Uraplex; ***Irl.:*** Regurin; ***Israel:*** Spasmex; ***Ital.:*** Uraplex; ***Port.:*** Spasmoplex; ***Rus.:*** Spasmex (Спазмекс); ***S.Afr.:*** Uricon; ***Spain:*** Uraplex; ***Switz.:*** Spasmo-Urgenine Neo; ***Thai.:*** Spasmo-Lyt; ***Turk.:*** Spasmex; ***UK:*** Regurin; ***USA:*** Sanctura.

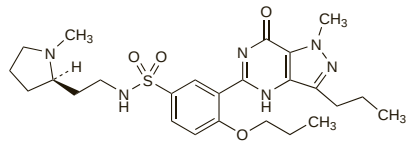
Multi-ingredient: *Arg.:* Keptan Compuesto†; ***Austria:*** Spasmo-Urgenin; ***Port.:*** Spasmo-Urgenin†; ***S.Afr.:*** Spasmo-Urgenin†; ***Spain:*** Spasmo-Urgenin; ***Thai.:*** Spasmo-Urgenin.

Udenafil *(rINN)*
DA-8159; Udénafil; Udenafilo; Udenafilum. 3-(1-Methyl-7-oxo-3-propyl-4,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-*N*-{2-[(2*RS*)-1-methylpyrrolidin-2-yl]ethyl}-4-propoxybenzenesulfonamide.

Уденафил

$C_{25}H_{36}N_6O_4S$ = 516.7.

CAS — 268203-93-6.



Profile
Udenafil is a phosphodiesterase type-5 inhibitor with actions and uses similar to those of sildenafil (p.2195). It is used in the management of erectile dysfunction.

Vardenafil *(rINN)*
Vardénafil; Vardenafilum. 1-{[3-(3,4-Dihydro-5-methyl-4-oxo-7-propylimidazo[5,1-*f*]-*as*-triazin-2-yl)-4-ethoxyphenyl]sulfonyl}-4-ethylpiperazine.

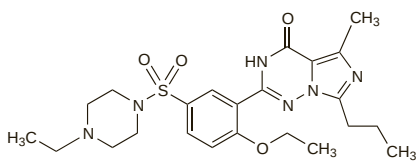
Варденафил

$C_{23}H_{32}N_6O_4S$ = 488.6.

CAS — 224785-90-4.

ATC — G04BE09.

ATC Vet — QG04BE09.



Vardenafil Dihydrochloride *(USAN, rINNM)*
Dihidrocloruro de vardenafil; Vardénafil, Dichlorhydrate de; Vardenafili Dihydrochloridum.

Варденафила Дигидрохлорид

$C_{23}H_{32}N_6O_4S,2HCl$ = 561.5.

CAS — 224789-15-5.

ATC — G04BE09.

ATC Vet — QG04BE09.

Vardenafil Hydrochloride *(USAN, rINNM)*
Bay-38-9456; Hidrocloruro de vardenafil; Vardénafil, Chlorhydrate de; Vardenafil Monohydrochloride; Vardenafili Hydrochloridum.

Варденафила Гидрохлорид

$C_{23}H_{32}N_6O_4S,HCl$ = 525.1.

CAS — 224785-91-5.

ATC — G04BE09.

ATC Vet — QG04BE09.

Adverse Effects and Precautions
As for Sildenafil, p.2193. Photosensitivity has also been reported. Vardenafil may prolong the QT interval and is best avoided in patients with relevant risk factors such as hypokalaemia, congenital QT prolongation, or the use of antiarrhythmics of class Ia or class III. Dosage reductions may be required in patients with hepatic or renal impairment.

Effects on the cardiovascular system. References.

1. Thadani U, *et al.* The effect of vardenafil, a potent and highly selective phosphodiesterase-5 inhibitor for the treatment of erectile dysfunction, on the cardiovascular response to exercise in patients with coronary artery disease. *J Am Coll Cardiol* 2002; **40:** 2006–12.

Interactions
As for Sildenafil, p.2194. The use of vardenafil with potent inhibitors of the cytochrome P450 isoenzyme CYP3A4 (such as HIV-protease inhibitors, some azole antifungals, and macrolide antibacterials) is generally best avoided; if thought to be essential, dosage of vardenafil must be reduced and suggested doses are given below (p.2199). Use with ketoconazole and itraconazole is contra-indicated in men older than 75 years of age. An enhanced hypotensive effect may be seen if vardenafil is taken with nifedipine. Vardenafil may prolong the QT interval and its use with antiarrhythmics of class Ia or class III should be avoided.

Pharmacokinetics
Vardenafil is rapidly absorbed after an oral dose, with a bioavailability of about 15%. Peak plasma concentrations are attained within 30 to 120 minutes; the rate of absorption is reduced when vardenafil is given with a high-fat meal.

Vardenafil is widely distributed into tissues and is about 95% bound to plasma proteins. It is metabolised in the liver primarily by cytochrome P450 isoenzymes CYP3A4 (the major route) as well as CYP3A5 and CYP2C isoforms. The major metabolite produced by desethylation of vardenafil also has some activity. The terminal half-life is about 4 to 5 hours.

Vardenafil is excreted as metabolites mainly in the faeces (91 to 95%), and to a lesser extent in the urine (2 to 6%). Clearance may be reduced in the elderly and in patients with hepatic or severe renal impairment.

◊ References.

1. Rajagopalan P, *et al.* Effect of high-fat breakfast and moderate-fat evening meal on the pharmacokinetics of vardenafil, an oral phosphodiesterase-5 inhibitor for the treatment of erectile dysfunction. *J Clin Pharmacol* 2003; **43:** 260–7.
2. Gupta M, *et al.* The clinical pharmacokinetics of phosphodiesterase-5 inhibitors for erectile dysfunction. *J Clin Pharmacol* 2005; **45:** 987–1003.

Uses and Administration
Vardenafil is a phosphodiesterase type-5 inhibitor with actions and uses similar to those of sildenafil (p.2195). It is used in the management of erectile dysfunction (p.2179). Vardenafil is given orally as the hydrochloride trihydrate although doses are expressed in terms of