el; Omnic†; Omsil; Tamsu; ***Israel:*** Omnic; ***Ital.:*** Omnic; Pradif; ***Jpn:*** Harnal; ***Mex.:*** Asoflon; Secotex; ***Neth.:*** Mapelor; Omnic; ***Norw.:*** Omnic; ***NZ:*** Flomax; Flomaxtra; ***Philipp.:*** Harnal; ***Pol.:*** Bazetham; Fokusin; Omnic; Omsal; Prostamnic; Tamsudil; TamsuLek; Tanyz; Uprox; Urostad; ***Port.:*** Omnic; Pradif; ***Rus.:*** Fokusin (Фокусин); Hyperprost (Гиперпрост); Omnic (Омник); ***S.Afr.:*** Flomax; ***Spain:*** Omnic; Urolosin; ***Switz.:*** Omix; Pradif; ***Thai.:*** Harnal; ***Turk.:*** Flomax; ***UK:*** Bazetham; Contiflo; Flomax†; Flomaxtra; Stronazon; Tabphyn; ***USA:*** Flomax; ***Venez.:*** Secotex; Tamsulon.

Multi-ingredient: ***India:*** Urimax F.

Tolterodine Tartrate *(BANM, USAN, rINNM)*

Kabi-2234 (tolterodine); PNU-200583E; Tartrato de tolterodina; Tolterodin Tartrat; Tolterodine L-Tartrate; Toltérodine, Tartrate de; Tolterodini Tartras. (+)-(*R*)-2-{α-[2-(Diisopropylamino)ethyl]benzyl}-*p*-cresol tartrate.

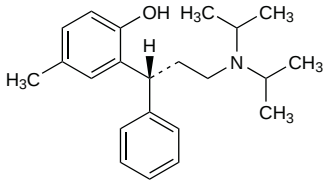
Тольтеродина Тартрат

$C_{22}H_{31}NO,C_4H_6O_6$ = 475.6.

CAS — 124937-51-5 (tolterodine); 124937-52-6 (tolterodine tartrate).

ATC — G04BD07.

ATC Vet — QG04BD07.



(tolterodine)

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p.1219. For a report of adverse ocular effects of tolterodine, see Effects on the Eyes under Oxybutynin, p.2190. Tolterodine should be used with caution in patients with hepatic or renal impairment. *Animal* studies have shown that high doses may cause fetal toxicity and it is recommended that tolterodine should be avoided during pregnancy.

Prolongation of the QT interval has occurred in controlled studies using both therapeutic and higher doses of tolterodine, and although changes from baseline did not cross the threshold of concern, the clinical implications are unclear. Licensed product information therefore warns that tolterodine should be used with caution in patients with QT prolongation or relevant risk factors, such as electrolyte disturbances, bradycardia, pre-existing cardiac disease, or the concomitant use of other drugs known to prolong the QT interval. Patients with raised tolterodine concentrations because of drug interactions (see below) would also be at increased risk, particularly poor metabolisers (see Pharmacokinetics, below).

◊ References.

1. Layton D, *et al.* Safety profile of tolterodine as used in general practice in England: results of prescription-event monitoring. *Drug Safety* 2001; **24:** 703–13.
2. Garely AD, Burrows L. Benefit-risk assessment of tolterodine in the treatment of overactive bladder in adults. *Drug Safety* 2004; **27:** 1043–57.

Interactions

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

There is a risk of interactions between tolterodine and drugs that inhibit cytochrome P450 isoenzymes CYP2D6 (but see Antidepressants, below), or CYP3A4. For comment on dosage of tolterodine with potent CYP3A4 inhibitors (such as the macrolide antibacterials erythromycin or clarithromycin, or the azole antifungals ketoconazole, itraconazole, or miconazole), see Uses and Administration, below. Tolterodine can prolong the QT interval and should be used with caution in patients receiving other drugs known to have this effect, particularly class Ia and class III antiarrhythmics.

Anticholinesterases. For mention of an interaction between tolterodine and *donepezil* or *rivastigmine*, see Antimuscarinics, under Donepezil, p.365.

Anticoagulants. For reference to the effect of tolterodine on the activity of *warfarin*, see under Antimuscarinics, p.1429.

Antidepressants. The SSRI *fluoxetine* is a potent inhibitor of the cytochrome P450 isoenzyme CYP2D6 and use with tolterodine has resulted in more than a fourfold increase in the area under the serum concentration-time curve (AUC) of tolterodine, associated with an approximate 20% decrease in the AUC of its 5-hydroxymethyl metabolite.[1] However, since both are active these changes were thought likely to result in little clinical difference, and licensed product information does not recommend a dose adjustment when tolterodine is given with fluoxetine.

1. Brynne N, *et al.* Fluoxetine inhibits the metabolism of tolterodine—pharmacokinetic implications and proposed clinical relevance. *Br J Clin Pharmacol* 1999; **48:** 553–63.

Gastrointestinal drugs. In a study[1] in healthy subjects, a dose of *antacid* was found to speed up the release of tolterodine from a modified-release preparation, probably as a result of the increase in gastric pH. Plasma-tolterodine concentrations were increased, but the half-life and area under the plasma concentration-time curve were not significantly affected. *Omeprazole* was reported to have a similar effect in another study.[2] The possible clinical effect of this change in drug release is unclear.

1. Sathyan G, *et al.* Effect of antacid on the pharmacokinetics of extended-release formulations of tolterodine and oxybutynin. *Clin Pharmacokinet* 2004; **43:** 1059–68.
2. Dmochowski R, *et al.* Effect of the proton pump inhibitor omeprazole on the pharmacokinetics of extended-release formulations of oxybutynin and tolterodine. *J Clin Pharmacol* 2005; **45:** 961–8.

Pharmacokinetics

Peak plasma concentrations of tolterodine occur 1 to 3 hours after an oral dose. It is highly bound to plasma proteins. Tolterodine is mainly metabolised in the liver by the cytochrome P450 isoenzyme CYP2D6 to the active 5-hydroxymethyl derivative (DD-01); in a minority of poor metabolisers tolterodine is metabolised by CYP3A4 isoenzymes to its inactive *N*-dealkylated derivative. The absolute bioavailability of tolterodine is normally about 17%, and the half-life is 2 to 3 hours; these increase in poor metabolisers to an absolute bioavailability of 65% and a half-life of about 10 hours. However, the clinical use of tolterodine is not affected by these differences in metabolism because the exposure to unbound tolterodine in poor metabolisers is similar to the combined exposure to unbound tolterodine and the active 5-hydroxymethyl metabolite in extensive metabolisers. Tolterodine is excreted primarily in the urine with about 17% appearing in the faeces; less than 1% of a dose is excreted as unchanged drug.

◊ References.

1. Brynne N, *et al.* Pharmacokinetics and pharmacodynamics of tolterodine in man: a new drug for the treatment of urinary bladder overactivity. *Int J Clin Pharmacol Ther* 1997; **35:** 287–95.
2. Brynne N, *et al.* Influence of CYP2D6 polymorphism on the pharmacokinetics and pharmacodynamics of tolterodine. *Clin Pharmacol Ther* 1998; **63:** 529–39.

Uses and Administration

Tolterodine tartrate is a tertiary 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. Tolterodine is used in the management of urinary frequency, urgency, and incontinence in detrusor instability. Usual oral doses of tolterodine tartrate are 2 mg twice daily; modified-release preparations are given in a usual dose of 4 mg once daily. Doses of 1 mg twice daily (or 2 mg daily as a modified-release preparation) are recommended in patients experiencing troublesome adverse effects. The *BNFC* suggests that a dose of 1 mg daily, increased according to response to a maximum of 2 mg twice daily, may be used in children from 2 years of age. Licensed US product information advises that the dose of tolterodine should not exceed 2 mg daily in patients receiving potent CYP3A4 inhibitors; UK product information recommends against such combinations. See also below for doses in patients with hepatic or renal impairment.

Administration in hepatic or renal impairment. Oral doses of 1 mg of tolterodine tartrate twice daily (or 2 mg daily as a modified-release preparation) are recommended by UK and US licensed product information in patients with hepatic or severe renal impairment.

Urinary incontinence. Tolterodine is used as an alternative to oxybutynin in the treatment of urge incontinence (see p.2180). Tolterodine is said to have fewer adverse effects than oxybutynin, but these may be comparable to modified-release oxybutynin.

References.

1. Harvey M-A, *et al.* Tolterodine versus oxybutynin in the treatment of urge urinary incontinence: a meta-analysis. *Am J Obstet Gynecol* 2001; **185:** 56–61.
2. Jacquetin B, Wyndaele J. Tolterodine reduces the number of urge incontinence episodes in patients with an overactive bladder. *Eur J Obstet Gynecol Reprod Biol* 2001; **98:** 97–102.
3. Sussman D, Garely A. Treatment of overactive bladder with once-daily extended-release tolterodine or oxybutynin: the antimuscarinic clinical effectiveness trial (ACET). *Curr Med Res Opin* 2002; **18:** 177–84.
4. Swift S, *et al.* A new once-daily formulation of tolterodine provides superior efficacy and is well tolerated in women with overactive bladder. *Int Urogynecol J Pelvic Floor Dysfunct* 2003; **14:** 50–4.
5. Diokno AC, *et al.* Prospective, randomized, double-blind study of the efficacy and tolerability of the extended-release formulations of oxybutynin and tolterodine for overactive bladder: results of the OPERA trial. *Mayo Clin Proc* 2003; **78:** 687–95.
6. Khullar V, *et al.* Treatment of urge-predominant mixed urinary incontinence with tolterodine extended release: a randomized, placebo-controlled trial. *Urology* 2004; **64:** 269–74.
7. Sand PK, *et al.* A comparison of extended-release oxybutynin and tolterodine for treatment of overactive bladder in women. *Int Urogynecol J Pelvic Floor Dysfunct* 2004; **15:** 243–8.
8. Nijman RJ, *et al.* Tolterodine treatment for children with symptoms of urinary urge incontinence suggestive of detrusor overactivity: results from 2 randomized, placebo controlled trials. *J Urol (Baltimore)* 2005; **173:** 1334–9.
9. Rovner ES. Tolterodine for the treatment of overactive bladder: a review. *Expert Opin Pharmacother* 2005; **6:** 653–66.
10. 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)
Arg.: Breminal; Detrusitol; Toltem; Urginol; ***Austral.:*** Detrusitol; ***Austria:*** Detrusitol; Detsel; ***Belg.:*** Detrusitol; ***Braz.:*** Detrusitol; ***Canad.:*** Detrol; Unidet; ***Chile:*** Detrusitol; ***Cz.:*** Detrusitol; ***Denm.:*** Detrusitol; ***Fin.:*** Detrusitol; ***Fr.:*** Detrusitol; ***Ger.:*** Detrusitol; ***Gr.:*** Detrusitol; ***Hong Kong:*** Detrusitol; ***Hung.:*** Detrusitol; ***India:*** Detrusitol; Terol; ***Indon.:*** Detrusitol; ***Irl.:*** Detrusitol; ***Israel:*** Detrusitol; ***Ital.:*** Detrusitol; ***Malaysia:*** Detrusitol; ***Mex.:*** Detrusitol; ***Neth.:*** Detrusitol; Detsel†; ***Norw.:*** Detrusitol; ***NZ:*** Detrusitol; ***Pol.:*** Detrusitol; ***Port.:*** Detrusitol; ***Rus.:*** Detrusitol (Детрузитол); ***S.Afr.:*** Detrusitol; ***Singapore:*** Detrusitol; ***Spain:*** Detrusitol; Urotrol; ***Swed.:*** Detrusitol; ***Switz.:*** Detrusitol; ***Thai.:*** Detrusitol; ***Turk.:*** Detrusitol; ***UK:*** Detrusitol; ***USA:*** Detrol; ***Venez.:*** Detrusitol.

Trospium Chloride *(BAN, USAN, rINN)*

Cloruro de trospio; IP-631; Trospii chloridum; Trospio cloridas; Trospium, chlorure de; Trospium-chlorid; Trospiumklorid; Trospiumkloridi; Trospiyum Klorür. 3α-Benziloyloxynortropane-8-spiro-1′-pyrrolidinium chloride.

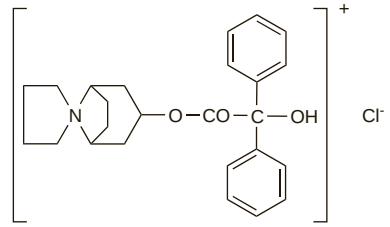
Троспия Хлорид

$C_{25}H_{30}ClNO_3$ = 428.0.

CAS — 10405-02-4.

ATC — G04BD09.

ATC Vet — QG04BD09.



Pharmacopoeias. In *Eur.* (see p.vii)
Ph. Eur. 6.2 (Trospium Chloride). A white or almost white, crystalline powder. Very soluble in water; practically insoluble in dichloromethane; freely soluble in methyl alcohol. A 1% solution in water has a pH of 5.0 to 7.0. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p.1219. Trospium should be used with caution in patients with hepatic or renal impairment. *Animal* studies have shown that trospium crosses the placenta and is distributed into breast milk; licensed product information therefore recommends that caution should be observed during pregnancy and breast feeding.

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.

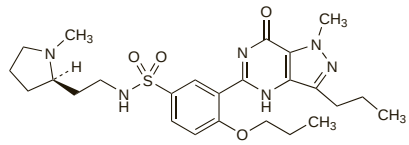
Multi-ingredient: *Arg.:* Keptan Compuesto†; ***Austria:*** Spasmo-Urgenin; ***Port.:*** Spasmo-Urgenin†; ***S.Afr.:*** Spasmo-Urgenin†; ***Spain:*** Spasmo-Urgenin; ***Thai.:*** Spasmo-Urgenin.

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.

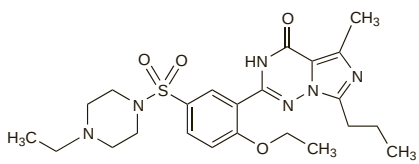
Варденафил

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