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.

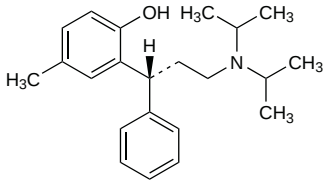
Тольтеродина Тартрат

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

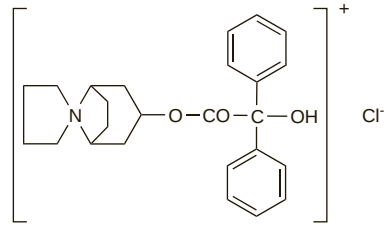
Троспия Хлорид

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