PRODUCT INFORMATION

DETRUSITOL® tablets 1 mg and 2 mg

DETRUSITOL tablets contain the active substance tolterodine tartrate, a competitive muscarinic receptor antagonist.

NAME OF THE DRUG

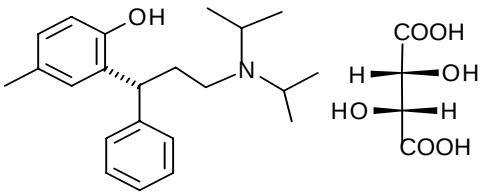
Non-proprietary name: tolterodine tartrate

Chemical name: (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine L-hydrogen tartrate

CAS No: 124937-52-6

DESCRIPTION

Tolterodine has one chiral centre, and it is obtained as a pure (+)-isomer by fractional crystallisation as the L-tartaric acid salt with a molecular formula $C_{26}H_{37}NO_7$ and a molecular weight of 475.58. The structural formula of tolterodine tartrate is represented below:



Tolterodine tartrate is a white, odourless, crystalline powder. It is sparingly soluble in water, soluble in methanol, slightly soluble in ethanol, and practically insoluble in toluene. The solubility in water has a minimum at pH 3 to 3.5, where the solubility is 4.7 mg/mL.

PHARMACOLOGY

Tolterodine is a competitive muscarinic receptor antagonist. Both urinary bladder contraction and salivation are mediated via cholinergic muscarinic receptors.

After oral administration, tolterodine is metabolised in the liver, resulting in the formation of the 5-hydroxymethyl derivative (DD01), a major pharmacologically active metabolite. The DD01 metabolite, which exhibits an antimuscarinic activity similar to that of tolterodine, contributes significantly to the therapeutic effect. Both tolterodine and DD01 exhibit a high specificity for muscarinic receptors, since both show negligible activity or affinity for other neurotransmitter receptors and other potential cellular targets, such as calcium channels.

The main effects of tolterodine on urodynamic parameters at 1 and 5 hours after administration, as determined in healthy volunteers, were an increase in residual urine, reflecting an incomplete emptying of the bladder, and a decrease in detrusor pressure. These findings are consistent with an antimuscarinic action on the lower urinary tract.

Non-clinical QT Interval Data

Tolterodine, its 5-hydroxymethyl metabolite (DD01), and its N-dealkylated metabolite have been shown to prolong action potential duration (90% repolarisation) in canine Purkinje fibres (14 to 75 times therapeutic $Cmax_{unbound}$) and block the K+ current in cloned human ether-a-go-go-related gene (hERG) channels (0.5 to 10 times therapeutic $Cmax_{unbound}$). In dogs, prolongation of the QT interval has been observed after application of tolterodine and its human metabolites at 3 to 42 times therapeutic $Cmax_{unbound}$. The clinical relevance of these findings is unknown. (See **PRECAUTIONS**).

Pharmacokinetics

Absorption

Tolterodine is rapidly absorbed and reaches its maximum serum concentrations 1-2 hours after dose administration. The average peak serum concentration increases proportionally in the dose interval 1 to 4 mg. Food intake increases the bioavailability of tolterodine (average increase 53%) but does not affect the levels of DD01 in EM. This change is not expected to be a safety concern and adjustment of dose is not needed.

Distribution

Tolterodine is highly bound to plasma proteins, primarily α_1-acid glycoprotein. Unbound concentrations of tolterodine average 3.7% over the concentration range achieved in clinical studies. DD01 is not extensively protein bound, with unbound fraction concentrations averaging 36% ± 4%. The blood to serum ratio of tolterodine and DD01 averages 0.6 and 0.8 respectively, indicating that these compounds do not distribute extensively into erythrocytes. The volume of distribution of tolterodine following administration of a 1.28 mg intravenous dose is 113 ± 26.7 L.

Metabolism

Tolterodine is extensively metabolised by the liver following oral dosing. The primary metabolic route involves the oxidation of the 5-methyl group and is mediated by the isoenzyme cytochrome P450 2D6 leading to the formation of the pharmacologically active metabolite DD01. Further metabolism leads to formation of the 5-carboxylic acid and N-dealkylated 5-carboxylic acid metabolites, which account for 51% ± 14% and 29% ± 6.3%, respectively, of the metabolites recovered in the urine.

A subset (about 7%) of the population is devoid of the drug-metabolising isoenzyme cytochrome P450 2D6, responsible for the formation of the 5-hydroxymethyl metabolite DD01 of tolterodine. The identified pathway of metabolism for these individuals, referred to as ‘poor metabolisers’ (PM), is dealkylation via cytochrome P450 3A4 to N-dealkylated tolterodine. The remainder of the population is referred to as ‘extensive metabolisers’.

Pharmacokinetic studies revealed that tolterodine is metabolised at a slower rate in poor metabolisers than in extensive metabolisers. This results in significantly higher serum concentrations of tolterodine and in negligible concentrations of DD01. Because of differences in the protein-binding characteristics of tolterodine and DD01, the sum of unbound serum concentrations of tolterodine and DD01 is similar in extensive and poor metabolisers at steady state. Since tolterodine and DD01 have similar antimuscarinic effects, the net activity of DETRUSITOL tablets is expected to be similar in extensive and poor metabolisers. (Also see **PRECAUTIONS, Drug Interactions, *Cytochrome P450 3A4 inhibitors***).

Excretion

The primary route of elimination for tolterodine is by hepatic metabolism.

Following administration of a 5 mg oral dose of [^{14}C]-tolterodine to healthy volunteers, 77% of radioactivity was recovered in urine and 17% was recovered in faeces. Less than 1% (<2.5% in poor metabolisers) of the dose was recovered as intact tolterodine and 5% to 14% (<1% in poor metabolisers) was recovered as the active DD01 metabolite. Most of the radioactivity was recovered in the first 24 hours, which is consistent with the apparent half-life of tolterodine: 1.9 to 3.7 hours in pharmacokinetic studies.

A summary of mean (± standard deviation) pharmacokinetic parameters of tolterodine and DD01 in EMs and PMs is provided in Table 1. These data were obtained following single and multiple doses of tolterodine 4 mg administered daily to 16 healthy male subjects (8 EM, 8 PM).

Table 1: Summary of mean (± SD) pharmacokinetic parameters of tolterodine and DD01

	Tolterodine					DD01			
Phenotype	t_{max} (h)	C_{max}* (µg/L)	C_{avg}* (µg/L)	$t_{1/2}$ (h)	Cl/F (L/h)	t_{max} (h)	C_{max}* (µg/L)	C_{avg}* (µg/L)	$t_{1/2}$ (h)
Single-dose									
EM	1.6±1.5	1.6±1.2	0.50±0.35	2.0±0.7	534±697	1.8±1.4	1.8±0.7	0.62±0.26	3.1±0.7
PM	1.4±0.5	10±4.9	8.3±4.3	6.5±1.6	17±7.3	-	-	-	-
Multi-dose									
EM	1.2±0.5	2.6±2.8	0.58±0.54	2.2±0.4	415±377	1.2±0.5	2.4±1.3	0.92±0.46	2.9±0.4
PM	1.9±1.0	19±7.5	12±5.1	9.6±1.5	11±4.2	-	-	-	-

SD=Standard Deviation
* Parameter was dose-normalised from 4 mg to 2 mg
C_{max} = Maximum plasma concentration; t_{max} = Time of occurrence of C_{max}
C_{avg} = Average plasma concentration; $t_{1/2}$= Terminal elimination half-life
Cl/F = Apparent oral clearance
- = Not applicable

Pharmacokinetics in Special Populations

Age

In phase I multiple-dose studies in which tolterodine 2 mg was administered twice daily, serum concentrations of tolterodine and of DD01 were similar in healthy elderly volunteers (aged 64 through 80 years) and healthy young volunteers (aged less than 40 years). In another phase I study, elderly volunteers (aged 71 through 81 years) were given tolterodine 1

or 2 mg twice daily. Mean serum concentrations of tolterodine and DD01 in these elderly volunteers were approximately 20% and 50% higher, respectively, than reported in young healthy volunteers. However, no overall differences were observed in safety between older and younger patients in phase III, 12-week, controlled clinical studies; and therefore, no dosage adjustment is recommended (see PRECAUTIONS, Geriatric Use).

Paediatric

The pharmacokinetics of tolterodine have not been established in paediatric patients.

Gender

Pharmacokinetic data from three Phase I clinical studies (Studies 022, 024, and 028) in which a tolterodine dose of 2 mg was administered in the fasting state were analysed with respect to gender. The pharmacokinetics of tolterodine and DD01 are not influenced by gender. Mean Cmax of tolterodine (1.6 μg/L in males versus 2.2 μg/L in females) and DD01 (2.2 μg/L in males versus 2.5 μg/L in females) are similar in males and females who were administered tolterodine 2 mg. Mean AUC values of tolterodine (6.7 μg.h/L in males versus 7.8 μg.h/L in females) and DD01 (10 μg.h/L in males versus 11 μg.h/L in females) are also similar. The elimination half-life of tolterodine for both males and females is 2.4 hours, and the half-life of DD01 is 3.3 hours in males and 3.0 hours in females.

Race

Differences among races regarding metabolic capacity can be assumed to be of a quantitative nature and are probably less than the thoroughly documented difference between extensive and poor metabolisers. The few non-Caucasians included do not show a different pharmacokinetic profile of tolterodine or DD01.

Renal Insufficiency

The mean exposure of unbound tolterodine and its 5-hydroxymethyl metabolite is doubled in patients with severe renal impairment (inulin clearance GFR ≤ 30 mL/min). The plasma levels of other metabolites were markedly increased in these patients and individual levels 9 to 30-fold higher than placebo were observed. A 60-fold higher level of one metabolite was observed in one patient with poor metabolism. The clinical relevance of the increased exposure of these metabolites is unknown. There is no data in mild to moderate renal impairment. Patients with severe renal impairment should not receive doses of greater than 1 mg twice daily (see **PRECAUTIONS**).

Hepatic Insufficiency

As might be predicted from a drug in which hepatic metabolism is the primary route of elimination, liver impairment can significantly alter the disposition of tolterodine. In a study of cirrhotic patients, elimination half-life of tolterodine was longer in cirrhotic patients (mean, 8.7 hours) than in healthy, young and elderly volunteers (mean, 2 to 4 hours). The clearance of orally administered tolterodine was substantially lower in cirrhotic patients (1.1 ± 1.7 L/h.kg) than in the healthy volunteers (5.7 ± 3.8 L/h.kg). Patients with significantly reduced hepatic function should not receive doses of greater than 1 mg twice daily (see **PRECAUTIONS**).

CLINICAL TRIALS

DETRUSITOL tablets were evaluated for the treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence, or any combination of these symptoms in four 12-week controlled studies (study numbers 008, 009, 010 and 015). Two studies (008 and 010) compared DETRUSITOL 2 mg twice daily (N=227) with oxybutynin 5 mg three times daily (N=230) and placebo (N=113). A third study (009) compared DETRUSITOL 1 mg (N=123) and 2 mg (N=129) twice daily and placebo (N=64). The fourth study (015) compared DETRUSITOL 2 mg twice daily (N=120) and oxybutynin 5 mg three times daily (N=120). The primary efficacy end point in these studies was the mean number of micturitions per 24 hours; secondary end points were the mean number of incontinence episodes per 24 hours, and the mean volume of urine voided per micturition. After 12 weeks of treatment, DETRUSITOL was shown to be significantly more effective than placebo in two of the three placebo-controlled studies in reducing the mean number of micturitions per 24 hours, and in all three placebo-controlled studies in increasing the mean volume voided per micturition (see Table 2).

None of the individual placebo-controlled studies demonstrated a statistically significant reduction in the number of incontinence episodes per 24 hours, when comparing DETRUSITOL with placebo. However, when pooled analyses for these studies were conducted, DETRUSITOL was significantly more effective than placebo. None of the placebo-controlled studies showed significant subjective improvement in bladder function from patient questionnaires.

Table 2: 95% Confidence Intervals (CI) for the Difference between DETRUSITOL 2 mg bid and Placebo for the Mean Change at Week 12 from Baseline in Studies 008, 009 and 010.

Study		Detrusitol (SD)	Placebo (SD)	Difference (95% CI)
Number of Micturitions per 24 Hours				
008	Number of patients	118	56	
	Mean baseline	11.5	11.7	
	Mean change from baseline	-2.7 (3.8)	-1.6 (3.6)	-1.2* (-2.0, -0.4)
009	Number of patients	128	64	
	Mean baseline	11.2	11.3	
	Mean change from baseline	-2.3 (2.1)	-1.4 (2.8)	-0.9* (-1.5, -0.3)
010	Number of patients	108	56	
	Mean baseline	11.6	11.6	
	Mean change from baseline	-1.7 (2.3)	-1.4 (2.8)	-0.38 (-1.1, 0.3)
Number of Incontinence Episodes per 24 Hours				
008	Number of patients	93	40	
	Mean baseline	2.9	3.3	
	Mean change from baseline	-1.3 (3.2)	-0.9 (1.5)	0.5 (-1.3, 0.3)
009	Number of patients	116	55	
	Mean baseline	3.6	3.5	
	Mean change from baseline	-1.7 (2.5)	-1.3 (2.5)	-0.4 (-1.0, 0.2)
010	Number of patients	90	50	
	Mean baseline	3.7	3.5	
	Mean change from baseline	-1.6 (2.4)	-1.1 (2.1)	-0.5 (-1.1, 0.1)
Volume voided per Micturition (mL)				
008	Number of patients	118	56	
	Mean baseline	166	157	
	Mean change from baseline	38 (54)	6 (42)	32*(18,46)
009	Number of patients	129	64	
	Mean baseline	155	158	
	Mean change from baseline	36 (50)	10 (47)	26* (14, 38)
010	Number of patients	108	56	
	Mean baseline	155	160	
	Mean change from baseline	31 (45)	13 (52)	18* (4, 32)

SD = Standard Deviation
*The difference between DETRUSITOL and placebo was statistically significant

In the three active comparator studies, DETRUSITOL and oxybutynin were equivalent in the reduction of mean number of micturitions per 24 hours and mean number of incontinence episodes per 24 hours. Significant improvement was seen after 2 weeks of treatment with DETRUSITOL, with further improvement up to 8 weeks of treatment; this therapeutic effect was sustained for up to 12 months of treatment.

Clinical QT Interval Data

A post-hoc pooled analysis of ECG data from 13 phase I-III clinical studies was conducted to assess the effect of tolterodine on QT interval. There were 102/468 (21.8%) patients in the tolterodine group who developed an increase in corrected QT interval of ≥30ms compared

with 18/141 (12.8%) in the placebo group. No subject experienced a QTc interval exceeding the potentially clinically relevant threshold of 500ms. No case of torsade de pointes was reported in this analysis, or in any of the tolterodine clinical studies. (Also see **ADVERSE REACTIONS, Post-marketing Experience** and **PRECAUTIONS, Drug Interactions, *Drugs Which Prolong the QT/QTc Interval***).

INDICATIONS

DETRUSITOL is indicated for the treatment of patients with overactive bladder with symptoms of urinary frequency, urgency or incontinence or any combination of these symptoms.

CONTRAINDICATIONS

DETRUSITOL is contraindicated in patients with urinary retention; gastric retention; uncontrolled narrow angle glaucoma; myasthenia gravis; severe ulcerative colitis; toxic megacolon. DETRUSITOL is also contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

PRECAUTIONS

Bladder Outflow Obstruction

DETRUSITOL should be used with caution in patients with clinically significant bladder outflow obstruction because of the risk of urinary retention.

Gastrointestinal Disorders

DETRUSITOL should be used with caution in patients with gastrointestinal obstructive disorders such as pyloric stenosis and in patients with autonomic neuropathy, hiatus hernia or decreased gastrointestinal motility.

Narrow Angle Glaucoma

DETRUSITOL should be used with caution in patients being treated for narrow angle glaucoma.

Visual Disturbance

Patients should also be informed that antimuscarinic agents may produce blurred vision or dizziness.

Hepatic Impairment

Patients with significantly reduced hepatic function should not receive doses of DETRUSITOL greater than 1 mg twice daily. (See **PHARMACOLOGY, Pharmacokinetics in Special Populations**).

Renal Impairment

Patients with severe renal impairment should not receive doses of DETRUSITOL greater than 1 mg twice daily. The potential toxicological effects of metabolites should be taken into account when exposing patients with severe renal impairment (especially poor metabolisers) to repeated doses of tolterodine. (See **PHARMACOLOGY, Pharmacokinetics in Special Populations**).

Cardiac Function

As with other drugs in this class, caution should be used in patients with known risk factors for QT prolongation (i.e. *congenital or documented acquired QT prolongation, hypokalaemia, *hypomagnesaemia, *hypocalcaemia, bradycardia, concurrent administration of drugs known to prolong the QT interval (See Drug Interactions, Drugs Which Prolong the QT/QTc Interval)) and relevant pre-existing cardiac diseases (i.e. myocardial ischaemia, arrhythmia, congestive heart failure, *cardiomyopathy). (See also **PHARMACOLOGY, Non-clinical QT Interval Data**).

Drug Interactions

Concomitant medication with other drugs that possess anticholinergic properties may result in more pronounced therapeutic effect and side-effects. Conversely, the therapeutic effect of tolterodine may be reduced by concomitant administration of muscarinic cholinergic receptor agonists. The effect of prokinetics like metoclopramide and cisapride may be decreased by tolterodine.

Clinical drug interaction studies have shown that:

Fluoxetine

Fluoxetine is a selective serotonin reuptake inhibitor and a potent inhibitor of cytochrome P450 2D6 activity. In a study to assess the effect of fluoxetine on the pharmacokinetics of tolterodine and its metabolites, it was observed that fluoxetine significantly inhibited the metabolism of tolterodine in extensive metabolisers, resulting in a 4.8-fold increase in tolterodine AUC. However, DD01 showed a 52% decrease in Cmax and a 20% decrease in AUC. Fluoxetine thus alters the pharmacokinetics in patients who would otherwise be EMs of tolterodine to resemble the pharmacokinetic profile in poor metabolisers. The sums of unbound serum concentrations of tolterodine and DD01 are 25% higher during the interaction. However, no dose adjustment is required when DETRUSITOL and fluoxetine are coadministered.

Other Drugs Metabolised by P450 2D6

DETRUSITOL is not expected to influence the pharmacokinetics of drugs that are metabolised by P450 2D6, such as flecainide, and tricyclic antidepressants; however, the potential effect of tolterodine on the pharmacokinetics of these drugs has not been formally evaluated.

Warfarin

In healthy volunteers, co-administration of DETRUSITOL 2 mg twice daily for 7 days and a single dose of warfarin 25 mg on day 4 had no effect on prothrombin time, Factor VII suppression, or on the pharmacokinetics of warfarin.

Oral Contraceptives

DETRUSITOL 2 mg twice daily has no effect on the pharmacokinetics of an oral contraceptive (ethinyl oestradiol 30 mg; levonorgestrel 150 mg) as evidenced by the monitoring of ethinyl oestradiol and levonorgestrel over a 2-month cycle in healthy female volunteers.

Diuretics

Coadministration of tolterodine up to 4 mg twice daily for up to 12 weeks with diuretic agents, such as indapamide, hydrochlorothiazide, triamterene, bendrofluazide, chlorothiazide, methyclothiazide or frusemide, did not cause any adverse electrocardiographic (ECG) effects in patients with overactive bladder.

Cytochrome P450 3A4 inhibitors

In both poor metabolisers (PM) and extensive metabolisers (EM), cytochrome P450 3A4 is involved as the primary metabolising enzyme (PM) or secondary metabolising enzyme (EM). In the presence of ketoconazole, the mean Cmax and AUC of tolterodine increased 1.9 and 2.2 fold, respectively, in poor metabolisers and the half-life of tolterodine increased by 50%. Based on these findings, other potent CYP3A4 inhibitors may also increase serum concentrations of tolterodine.

Therefore concomitant administration with potent CYP3A4 inhibitors such as macrolide antibiotics (erythromycin and clarithromycin), antifungal agents (ketoconazole, itraconazole and miconazole) and antiproteases (ritonavir and indinavir) is not recommended.

Drugs Which Prolong the QT/QTc Interval

There is no satisfactory information on the concurrent use of tolterodine with drugs known to prolong the QT/QTc interval. In the absence of such information on these combinations the potential risk of pathological QT/QTc prolongation resulting in arrhythmias cannot be ruled out. Drugs known to prolong the QT/QTc interval include: erythromycin, quinidine, procainamide, disopyramide, sotalol, amiodarone, cisapride, fluconazole, amitriptyline, haloperidol, chlorpromazine, thioridazine, pimozide, droperidol. (Also see **CLINICAL TRIALS, Clinical QT Interval Data**).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with tolterodine were conducted in mice and rats. At the maximum tolerated dose in mice (30 mg/kg/day), female rats (20 mg/kg/day), and male rats (30 mg/kg/day), AUC values obtained for tolterodine were 355, 291, and 462 μg.h/L, respectively. In comparison, the human AUC value for a 2 mg dose administered twice daily is estimated at 34 μg.h/L in extensive metabolisers and 209 μg.h/L in poor metabolisers. Thus, tolterodine exposure in the carcinogenicity studies was 9 to 14 fold higher than expected in humans with extensive metabolism and 1.4 to 2.2 fold higher in poor metabolisers. No increase in tumours was found in either mice or rats.

No mutagenic effects of tolterodine were detected in a battery of *in vitro* tests, including bacterial mutation assays (Ames test) in four strains of *Salmonella typhimurium* and in two strains of *Escherichia coli*, a gene mutation assay in L5178Y mouse lymphoma cells, and chromosomal aberration tests in human lymphocytes. Tolterodine was also negative *in vivo* on the bone marrow micronucleus test in the mouse.

In female mice treated for 2 weeks before mating and during gestation with 20 mg/kg/day (corresponding to AUC value of about 500 μg.h/L), neither effect on reproductive performance or fertility, nor any anomalies or malformations were seen. Based on AUC values, the systemic exposure was about 15 fold higher in animals than in humans. In male mice, a dose of 30 mg/kg/day did not induce any adverse effects on fertility.

Use in Pregnancy

Pregnancy Category: B3

In mice, tolterodine has been shown to cause embryolethality, reduce foetal weight, and increase the incidence of foetal abnormalities (cleft palate, digital abnormalities, intra-abdominal haemorrhage, and various skeletal abnormalities, primarily reduced ossification) when given at doses of greater than 20 mg/kg/day. At this dose, the AUC value was about 15 fold higher than in humans. Rabbits treated subcutaneously with the maximum possible dose (0.8 mg/kg/day) achieved an AUC of 100 μg.h/L, which is about three-fold higher than that resulting from the human dose. This dose did not result in any embryotoxicity or teratogenicity.

There are no studies of tolterodine in pregnant women. Therefore, DETRUSITOL should be used during pregnancy only if the potential benefit for the mother justifies the potential risk for the foetus.

Use in Lactation

It is not known whether tolterodine is excreted in human milk. Administration of DETRUSITOL should therefore be discontinued during nursing.

Paediatric Use

The safety and effectiveness of DETRUSITOL in paediatric patients have not been established.

Geriatric Use

Of the 1120 patients who were treated in the four phase III, 12-week clinical studies of DETRUSITOL, 474 (42%) were 65 to 91 years of age. No overall differences in safety were observed between the older and younger patients.

Effects on Ability to Drive and Use Machines

Since this drug may cause accommodation disturbances and influence reaction time, the ability to drive and use machines may be negatively affected. Patients should be advised to exercise caution.

ADVERSE REACTIONS

Clinical Trials

The clinical program for DETRUSITOL comprised 2398 patients who were treated with either DETRUSITOL (N=1619), oxybutynin (N=349), or placebo (N=430). No differences in the safety profile of tolterodine were identified based on age, gender, race, or metabolism. A total of 1120 patients were treated in four phase III, 12-week, controlled clinical studies with either DETRUSITOL 2 mg twice daily (N=474), DETRUSITOL 1 mg twice daily (N=121), oxybutynin 5 mg three times daily (N=349), or placebo (N=176). These four studies form the basis for the main evaluation of safety and are discussed below.

The percentage of patients reporting any adverse event in the 12-week studies was similar for DETRUSITOL 2 mg twice daily (75.5%), DETRUSITOL 1 mg twice daily (74.4%), and placebo (77.8%). The incidence of serious adverse events was similar among treatment groups (DETRUSITOL 1 and 2 mg twice daily, 3.7%; placebo, 3.4%). Dry mouth was the most frequently reported adverse event across all treatment groups. The only other adverse events reported that are considered to be dose related or treatment related (present in 1% of patients in either DETRUSITOL treatment group and that occurred at an incidence of at least twice the rate observed for placebo) were dyspepsia, headache, constipation, and xerophthalmia. Dry mouth, constipation, abnormal vision (accommodation abnormalities), urinary retention, and xerophthalmia are all expected side effects of antimuscarinic agents. The incidence of confusion among patients treated with DETRUSITOL twice daily was 0.6%.

Discontinuation of treatment due to adverse events in the 12-week studies was reported for 8.0% of patients treated with DETRUSITOL 2 mg twice daily, 5.7% of the patients treated with placebo, and 1.7% of the patients treated with DETRUSITOL 1 mg twice daily. The frequency of discontinuation due to adverse events was highest during the first 4 weeks of treatment for all treatment groups.

Table 3 lists the adverse events reported in ≥ 1% of the patients treated with DETRUSITOL 1 mg or 2 mg twice daily in the 12-week studies. The relationship to study medication for most of these events is uncertain; many are thought to represent spontaneous events reported by patients with bladder dysfunction (and other concomitant diseases) and are not necessarily causally related to DETRUSITOL.

Table 3: Incidence (%) of Adverse Events Reported in ≥ 1% of Patients Treated with DETRUSITOL (1 or 2 mg bid) in 12-Week, Phase III Clinical studies

Body System	Adverse Event*	DETRUSITOL 1 mg bid N=121 (%)	DETRUSITOL 2 mg bid N=474 (%)	Oxybutynin 5 mg tid N=349 (%)	Placebo N=176 (%)
Autonomic Nervous	abnormal accommodation	3.3	3.6	5.4	4.0
	dry mouth	24.0	39.6	78.2	15.9
	palpitation	6.6	0.4	2.3	2.8
General	allergy	1.7	0	0	0
	back pain	0.8	2.7	2.6	3.4
	chest pain	0	3.4	2.2	1.7
	fatigue	7.4	6.8	4.6	7.4
	headache	6.6	11.0	6.9	7.4
	influenza-like symptoms	2.6	4.4	3.7	6.3
	leg pain	3.3	0.6	0.9	0.6
	malaise	1.7	0	1.1	0
	pain	2.5	0	0	1.1
	fall	0	1.3	1.1	0
Central/Peripheral Nervous	migraine	1.7	0	0	1.1
	paraesthesia	0	1.1	0	0
	vertigo/dizziness	9.1	8.9	8.6	9.1
Gastrointestinal	abdominal pain	5.8	7.6	6.3	6.3
	constipation	5.8	6.5	9.5	4.5
	diarrhoea	5.8	4.0	5.2	6.3
	dyspepsia	1.7	5.9	11.2	1.7
	flatulence	0	1.3	3.4	0
	nausea	3.3	4.2	6.3	5.7
	ulcerated stomatitis	1.7	0	0	0
	vomiting/nausea	1.7	1.7	2.9	0.6
Respiratory	asthma	1.7	0	0	0
	bronchitis	0.8	2.1	0.6	0.6
	coughing	1.7	2.1	4.0	1.7
	dyspnoea	1.7	0.8	0.6	1.1
	pharyngitis	0	1.5	3.4	2.3
	rhinitis	1.7	1.1	0	1.1
	sinusitis	5.8	1.1	2.3	5.7
	URI	2.5	5.9	3.2	9.1
Urinary	dysuria	2.6	2.5	2.9	4.0
	micturition freq.	1.7	1.1	0	1.7
	urinary retention	0	1.7	6.9	2.8
	UTI	5.0	5.5	7.7	7.4
Skin/Appendages	acne	1.7	0	0	0
	pruritus	1.7	1.3	1.4	1.1
	rash/erythema	0	1.7	2.9	2.8
	skin dry	0	1.7	6.9	0
Musculoskeletal	arthralgia	2.6	2.3	1.1	2.8
Vision	abnormal vision	1.7	1.1	0	0
	xerophthalmia	1.7	3.8	3.7	1.7
Psychiatric	nervousness	0	1.1	0	0
	somnolence	2.5	3.0	1.7	1.7
Metabolic/ Nutritional	alk. phosphatase abnormal	1.7	0	0	0
	enzyme abnormality	1.7	0.8	0	2.3
	weight increase	0.8	1.5	0.6	1.1
Cardiovascular	abnormal ECG	1.7	0.4	0	1.1
	hypertension	2.6	1.5	1.7	0.6
Resistance	infection	0.8	2.1	1.4	1.1
Total Patients Reporting Adverse Events		**74.4**	**75.5**	**93.1**	**77.8**

* URI=upper respiratory infection, freq=frequency, UTI=urinary tract infection, alk=alkaline, ECG=electrocardiogram

Post-marketing Experience

The following adverse events have been reported in association with tolterodine use:

Body as a whole: anaphylactoid reactions, including angioedema (very rare).

Central & peripheral nervous systems: dizziness (common), convulsions (rare), memory impairment (uncommon)[†].

Cardiovascular: tachycardia, palpitations (rare), cardiac failure (very rare). There has been no substantive evidence of torsade de pointes attributable to tolterodine in post-marketing experience following administration to approximately 8 million patients.

Gastrointestinal tract: diarrhoea (common), gastro-oesophageal reflux (uncommon).

Skin: flushed skin (uncommon).

General: mild to moderate oedema (uncommon).

Psychiatric: disorientation (not known), confusion (not known), hallucinations (rare).

Common: ≥ 1% and < 10%
Uncommon: ≥ 0.1% and < 1%
Rare: ≥ 0.01% and < 0.1%
Very rare: < 0.01%

Other Events

In view of the pharmacological activity of this product, the following events may develop: paralytic ileus, ileus and gastrointestinal obstruction.

Cases of aggravation of symptoms of dementia (e.g. confusion, disorientation, delusion) have been reported after tolterodine therapy was initiated in patients taking cholinesterase inhibitors for the treatment of dementia.

DOSAGE AND ADMINISTRATION

The recommended oral dose for tolterodine tablets is 2 mg twice daily. The dose may be lowered to 1 mg twice daily based on individual response and tolerability. For patients with significantly reduced hepatic function or severely impaired renal function (GFR≤30 mL/min), the recommended dose is 1 mg twice daily (See **PRECAUTIONS**).

Concomitant administration with potent CYP3A4 inhibitors is not recommended (See **Drug Interactions*, Cytochrome P450 3A4 inhibitors***).

After 6 months the need for further treatment should be considered.

OVERDOSAGE

The highest dose of tolterodine given to human volunteers was 12.8 mg as single dose. The most severe adverse events observed were accommodation disturbances and micturition

difficulties. Overdosage with tolterodine can potentially result in severe central antimuscarinic effects. These effects may be delayed and cyclical.

A 27-month-old child who ingested five to seven DETRUSITOL 2 mg tablets was treated with a suspension of activated charcoal and was hospitalised overnight with symptoms of dry mouth. The child fully recovered.

Treatment of overdosage with DETRUSITOL should consist of activated charcoal. Activated charcoal is usually most effective when administered within 1-hour of ingestion, however this may be successful even if delayed as anticholinergics slow GI motility. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected. Ipecac-induced emesis is not recommended, and dialysis is not likely to be of benefit as tolterodine is highly protein-bound.

Treatments for symptoms of overdosage are recommended as follows. For severe central anticholinergic effects (hallucinations, severe excitation), an anticholinesterase agent, such as physostigmine, may be used. If excitation and convulsions occur, administer an anticonvulsant, such as diazepam. Patients with respiratory insufficiency should be given artificial respiration. Patients with tachycardia may be treated with a beta-blocker. Those with urinary retention may be catheterised. Patients with troublesome mydriasis may be placed in a dark room and/or treated with pilocarpine eye drops. Overdosage with DETRUSITOL may prolong the QTc interval, therefore, in the event of overdosage, ECG monitoring is recommended and standard supportive measures for managing QT prolongation should be adopted.

Contact the Poisons Information Centre for advice on the management of an overdose.

PRESENTATION

DETRUSITOL Tablets 1 mg, contain 1 mg of tolterodine tartrate as the active ingredient. The 1 mg tablet is white, round, biconvex, film-coated, engraved with arcs above and below the letters “TO”.

DETRUSITOL Tablets 2 mg, contain 2 mg of tolterodine tartrate as the active ingredient. The 2 mg tablet is white, round, biconvex film-coated, engraved with arcs above and below the letters “DT”.

Each tablet also contains the following ingredients: microcrystalline cellulose, calcium hydrogen phosphate, sodium starch glycollate, magnesium stearate, silica colloidal anhydrous hypromellose, stearic acid, and titanium dioxide.

DETRUSITOL Tablets 1 mg and 2 mg are supplied in the following forms:
Blister pack containing: 14, 28, 56 and 140 tablets
Bottles containing: 60 and 500 tablets

POISON SCHEDULE OF THE DRUG

S4

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
ABN 50 008 422 348
38-42 Wharf Road
West Ryde NSW 2114
Australia

TGA Approval Date: 18 October 2005

Date of most recent amendment: 13 February 2008

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*Refer to changes of clinical significance in Product Information