
Data Sheet

Name of Medicine

Arrow - Tolterodine 1 & Arrow - Tolterodine 2 Tablets

Tolterodine L-tartrate 1 mg & 2 mg tablets

Presentation

Arrow - Tolterodine 1 is presented as white to off white, round, biconvex, film coated tablets, debossed with "S16" on one side and plain on other side

Arrow – Tolterodine 2 is presented as white to off white, round, biconvex, film coated tablets, debossed with "S042" on one side and plain on other side.

Inactive Ingredients:

Arrow – Tolterodine 1 & Arrow – Tolterodine 2 also contains: microcrystalline cellulose (E460), Sodium starch glycolate (Type-A), colloidal silicon dioxide (E551), magnesium stearate (E572), hydroxypropyl methylcellulose (E464), titanium dioxide (E171), macrogol, Talc (E553b)

Uses

Actions

Tolterodine is a competitive, specific muscarinic receptor antagonist which exhibits a selectivity for the urinary bladder over salivary glands, which have been demonstrated in non-clinical pharmacological *in vivo* studies. One of the tolterodine metabolites (5-hydroxymethyl derivative) exhibits a pharmacological profile similar to that of the parent compound. In extensive metabolisers this metabolite contributes significantly to the therapeutic effect (see **Pharmacokinetics**).

The effect of treatment can be expected within 4 weeks.

Non-Clinical QT Interval Data

Tolterodine, as well as its active human metabolites prolong action potential duration (90% repolarization) in canine purkinje fibres (14 - 75 times therapeutic levels) and block the K⁺-current in cloned human ether-a-go-go-related gene (hERG) channels (0.5 - 9.8 times therapeutic levels). In dogs prolongation of the QT interval has been observed after application of tolterodine and its human metabolites (3.1 - 42 times therapeutic levels) (see **Clinical Trials - Clinical QT Interval Data**).

Clinical Trials

The effect of tolterodine was evaluated in patients, examined with urodynamic assessment at baseline and, depending on the urodynamic result, they were allocated to a urodynamic positive (motor urgency) or a urodynamic negative (sensory urgency) group. Within each group, the patients were randomized to receive either tolterodine or placebo. The study could not provide convincing evidence that tolterodine had effects over placebo in patients with sensory urgency.

Table 1. Effect of treatment with tolterodine 2 mg twice daily after 4 and 12 weeks, respectively, compared with placebo (pooled data).

Absolute change and percentage change relative to baseline.

Variable	4-week studies			12-week studies		
	tolterodine 2 mg b.i.d.	Placebo	Statistical significance vs. placebo	tolterodine 2 mg b.i.d.	Placebo	Statistical significance vs. placebo
Number of micturitions per 24 hours	-1.6 (-14%) n=392	-0.9 (-8%) n=189	*	-2.3 (-20%) n=354	-1.4 (-12%) n=176	**
Number of incontinence episodes per 24 hours	-1.3 (-38%) n=288	-1.0 (-26%) n=151	n.s.	-1.6 (-47%) n=299	-1.1 (-32%) n=145	*
Mean volume voided per micturition (ml)	+25 (+17%) n=385	+12 (+8%) n=185	***	+35 (+22%) n=354	+10 (+6%) n=176	***
Number of patients with no or minimal bladder problems after treatment (%)	16% n=394	7% n=190	**	19% n=356	15% n=177	n.s.

n.s.=not significant; *=p<0.05; **= p<0.01; ***= p<0.001

Clinical QT Interval Data

The effect of 2 mg BID and 4 mg BID of tolterodine immediate-release (tolterodine IR) tablets on the QT interval was evaluated in a 4-way crossover, double-blind, placebo- and active-controlled (moxifloxacin 400 mg QD) study in healthy male (N=25) and female (N=23) volunteers aged 18-55 years. There was an approximately equal representation of CYP2D6 extensive metabolisers (EMs) and poor metabolisers (PMs). The 4 mg BID dose of tolterodine IR (two times the highest recommended dose) was chosen because this dose results in tolterodine exposure similar to that observed upon co-administration of tolterodine 2 mg BID with potent CYP3A4 inhibitors in patients who are CYP2D6 poor metabolisers (see **Warnings and Precautions**, and **Overdosage**).

Table 2 summarizes the mean change from baseline to steady state in corrected QT interval (Fridericia's QTcF and population-specific QTcP) relative to placebo at the time of peak tolterodine (1 hour) and moxifloxacin (2 hour) concentrations. QT interval was measured manually and by machine, and data from both are presented. The reason for the difference between machine and manual read of QT interval is unclear

Table 2. Mean (CI) change in QTc from baseline to steady state (Day 4 of dosing) at Tmax (relative to placebo)

Drug/Dose	N	QTcF (msec) (manual)	QTcF (msec) (machine)	QTcP (msec) (manual)	QTcP (msec) (machine)
Tolterodine 2 mg BID ¹	48	5.01 (0.28, 9.74)	1.16 (-2.99, 5.30)	4.45 (-0.37, 9.26)	2.00 (-1.81, 5.81)
Tolterodine 4 mg BID ¹	48	11.84 (7.11, 16.58)	5.63 (1.48, 9.77)	10.31 (5.49, 15.12)	8.34 (4.53, 12.15)
Moxifloxacin 400 mg QD ²	45	19.26 ³ (15.49, 23.03)	8.90 (4.77, 13.03)	19.10 ³ (15.32, 22.89)	9.29 (5.34, 13.24)

¹ At Tmax of 1 hr; 95% Confidence Interval

² At Tmax of 2 hr; 90% Confidence Interval

³ The effect on QT interval with 4 days of moxifloxacin dosing in this QT trial may be greater than typically observed in QT trials.

The QT effect of tolterodine immediate-release tablets appeared greater for 8 mg/day (two times the therapeutic dose) compared to 4 mg/day. The effect of tolterodine 8 mg/day was not as large as that observed after four days of therapeutic dosing with the active control moxifloxacin.

There appeared to be a greater QTc interval increase in PMs than in EMs after tolterodine treatment in this study (see **Warnings and Precautions**, and **Overdosage**).

Pharmacokinetics

Tolterodine is rapidly absorbed. Both tolterodine and the 5-hydroxymethyl metabolite reach maximal serum concentrations 1-3 hours after dose. The half-life for tolterodine given as the tablet is 2-3 hours in extensive metabolisers and about 10 hours in poor metabolisers (devoid of CYP2D6). Steady state concentrations are reached within 2 days after administration of the tablets.

Food does not influence the exposure to the sum of the unbound tolterodine and the active 5-hydroxymethyl metabolite in extensive metabolisers, although the tolterodine levels increase when taken with food. Clinically relevant changes are likewise not expected in poor metabolisers.

Absorption

After oral administration tolterodine is subject to CYP2D6 catalysed first-pass metabolism in the liver, resulting in the formation of the 5-hydroxymethyl derivative, a major pharmacologically active metabolite. The absolute bioavailability of tolterodine is 17% in extensive metabolisers, the majority of the patients, and 65% in poor metabolisers (devoid of CYP2D6).

Distribution

Tolterodine and the 5-hydroxymethyl metabolite bind primarily to alpha-1-acid glycoprotein. The unbound fractions are 3.7% and 36%, respectively. The volume of distribution of tolterodine is 113 L.

Metabolism

Tolterodine is extensively metabolised by the liver following oral dosing. The primary metabolic route is mediated by the polymorphic enzyme CYP2D6 and leads to the formation of the 5-hydroxymethyl metabolite. The half-life of the 5-hydroxymethyl metabolite is 3-4 hours. Further metabolism leads to formation of the 5-carboxylic acid and N-dealkylated 5-carboxylic acid metabolites, which account for 51 % and 29 % of the metabolites recovered in the urine, respectively. A subset (about 7%) of the population is devoid of CYP2D6 activity. The identified pathway of metabolism for these individuals (poor metabolisers) is dealkylation via CYP3A4 to N-dealkylated tolterodine, which does not contribute to the clinical effect. The remainder of the population is referred to as extensive metabolisers. The systemic clearance of tolterodine in extensive metabolisers is about 30 L/h. In poor metabolisers the reduced clearance leads to significantly higher serum concentrations of tolterodine (about 7-fold) and negligible concentrations of the 5-hydroxymethyl metabolite are observed.

The 5-hydroxymethyl metabolite is pharmacologically active. Because of the differences in the protein-binding characteristics of tolterodine and the 5-hydroxymethyl metabolite, the exposure (AUC) of unbound tolterodine in poor metabolisers is similar to the combined exposure of unbound tolterodine and the 5-hydroxymethyl metabolite in patients with CYP2D6 activity given the same dosage regimen. The safety, tolerability and clinical response are similar irrespective of phenotype.

Excretion

The excretion of radioactivity after administration of ¹⁴C-tolterodine is about 77% in urine and 17% in faeces. Less than 1% of the dose is recovered as unchanged drug, and about 4% as the 5-hydroxymethyl metabolite. The carboxylated

metabolite and the corresponding dealkylated metabolite account for about 51% and 29% of the urinary recovery, respectively.

The pharmacokinetics is linear in the therapeutic dosage range.

Specific patient groups

Impaired hepatic function: About 2-fold higher exposure of unbound tolterodine and the 5-hydroxymethyl metabolite is found in subjects with liver cirrhosis (see **Dosage and Administration**, and **Warnings and Precautions**).

Impaired renal function: The mean exposure of unbound tolterodine and its 5-hydroxymethyl metabolite is doubled in patients with severe renal impairment (inulin clearance GFR \leq 30 ml/min). The plasma levels of other metabolites were markedly (up to 12-fold) increased in these patients. The clinical relevance of the increased exposure of these metabolites is unknown. There are no data in mild to moderate renal impairment (see **Dosage and Administration**, and **Warnings and Precautions**).

Indications

Arrow – Tolterodine 1 & Arrow Tolterodine 2 are indicated for the treatment of overactive bladder with symptoms of urinary urgency, frequency, and/or urge incontinence.

Dosage and Administration

The recommended dose is 2 mg b.i.d. In the case of troublesome side-effects the dose may be reduced from 2 mg to 1 mg b.i.d.

The recommended dose is 1 mg b.i.d. for patients with impaired renal function, impaired liver function, or receiving concomitant ketoconazole or other potent CYP3A4 inhibitors.

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

Safety and effectiveness in children have not been established.

Contraindications

Tolterodine is contraindicated in patients with:

- known hypersensitivity to tolterodine or any other component of the drug.
- urinary retention
- uncontrolled narrow angle glaucoma

Warnings and Precautions

Tolterodine should be used with caution in the following patients:

- at risk for urinary retention
- at risk for decreased gastrointestinal motility
- with impaired renal function. The recommended total daily dose is 2 mg (see **Dosage and Administration**, and **Pharmacokinetics – Specific Patient Groups**)
- with impaired hepatic function. The recommended total daily dose is 2 mg (see **Dosage and Administration**, and **Pharmacokinetics – Specific Patient Groups**).
- with myasthenia gravis

Cardiac Function - Clinical QT Interval Data

In a study of the effect of tolterodine immediate-release tablets on the QT interval, the effect on the QT interval appeared greater for 8 mg/day (two times the therapeutic dose) compared to 4 mg/day and was more pronounced in CYP2D6 poor metabolisers (PM) than extensive metabolisers (EMs) (see **Uses - Clinical Trials**).

The effect of tolterodine 8 mg/day was not as large as that observed after four days of therapeutic dosing with the active control moxifloxacin. However, the confidence intervals overlapped.

Doses of 2 mg twice daily (therapeutic) and 4 mg twice daily (supratherapeutic) tolterodine prolonged the QTc interval by a mean of 2.4 and 4.8 msec respectively, versus 9.9 msec for moxifloxacin in a controlled clinical study.

The clinical relevance of these findings is unknown and cannot be generalised to all patients under all circumstances. It is recommended that the following factors be considered before initiating therapy with tolterodine: patients with known risk factors for QT prolongation [i.e. hypokalaemia, bradycardia, concurrent administration of drugs known to prolong the QT interval, such as Class IA (e.g. quinidine, procainamide) and Class III (e.g. amiodarone, sotalol) anti-arrhythmics] and relevant pre-existing cardiac diseases (i.e. myocardial ischaemia, arrhythmia, congestive heart failure).

CYP3A4 Inhibitors

The recommended total daily dose of tolterodine is 2 mg for patients on concomitant medication with potent CYP3A inhibitors, such as macrolide antibiotics (e.g. erythromycin and clarithromycin) or azole antifungal agents (e.g. ketoconazole, itraconazole and miconazole) (see **Dosage and Administration** and **Interactions**).

Organic reasons for urge and frequency should be considered before treatment.

Pregnancy and lactation

Studies in pregnant mice have shown that high doses of tolterodine caused reduced foetal weight, embryoletality and increased incidence of foetal malformations.

There are no studies in pregnant women. Therefore, tolterodine should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the foetus (see **Further Information – Preclinical Safety Data**).

Use of tolterodine during lactation should be avoided since no data on excretion into breast milk in humans are available.

Effect on ability to drive and use machines

Since tolterodine 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 Effects

Tolterodine may cause mild-to-moderate antimuscarinic effects, like dryness of the mouth, dyspepsia and reduced lacrimation.

Clinical Trials

Adverse events considered potentially drug-related from studies of tolterodine are provided below.

≥ 10% Dry mouth

≥ 1% to 10% Headache, constipation, dizziness/vertigo, abdominal pain, dyspepsia, fatigue, dry eyes, somnolence, abnormal vision (including abnormal accommodation), flatulence, dysuria.

Chest pain, dry skin, bronchitis, increased weight.

<1% Urinary retention, confusion, gastro-oesophageal reflux, flushed skin, allergic reactions.

Post-marketing Surveillance

The following adverse events were reported during post-marketing surveillance:

Immune System Disorders: anaphylactoid reactions

Psychiatric Disorders: disorientation, hallucinations

Nervous System Disorders: memory impairment

Cardiac Disorders: tachycardia, palpitations

Gastrointestinal Disorders: diarrhoea

Skin and Subcutaneous Tissue Disorders: angioedema

General Disorders and Administration Site Conditions: peripheral oedema

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.

Drug Interactions

Pharmacokinetic interactions are possible with other drugs metabolised by or inhibiting cytochrome P450 2D6 (CYP2D6) or CYP3A4. Concomitant treatment with fluoxetine does not result in a clinically significant interaction.

Ketoconazole, a potent inhibitor of CYP3A4, significantly increased plasma concentrations of tolterodine when co-administered to poor metabolisers (i.e. persons devoid of CYP2D6 metabolic pathway). For patients receiving ketoconazole or other potent CYP3A4 inhibitors, the recommended total daily dose is 2 mg (see **Dosage and Administration**, and **Warnings and Precautions – CYP3A4 Inhibitors**).

Clinical studies have shown no interactions with warfarin or combined oral contraceptives (ethinylloestradiol/levonorgestrel).

A clinical study with marker drugs for the major P450 isoenzymes has not shown any evidence that the activity of CYP2D6, 2C19, 2C9, 3A4 or 1A2 will be inhibited by tolterodine.

Overdosage

The highest dose of tolterodine tartrate given to human volunteers was 12.8 mg as a 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 Arrow – Tolterodine 2 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 Arrow – Tolterodine 1 or Arrow – Tolterodine 2 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, or both.

A small increase in QTc interval was observed at a total daily dose of 8 mg, twice the recommended daily dose. Overdosage with Arrow – Tolterodine 1 or Arrow – Tolterodine 2 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 (see **Warnings and Precautions**, and **Uses – Clinical Trials**).

Contact the Poisons Information Centre (telephone number in Australia is 131 126 and in New Zealand is 0800 POISON or 0800 764 766) for advice regarding management of overdose.

Pharmaceutical Precautions

Instructions for Use/Handling

Nil

Incompatibilities

Nil

Shelf Life

36 months

Special Precautions for Storage

Store Below 25°C.

Medicine Classification

Prescription Medicine

Package Quantities

Arrow – Tolterodine 1 & Arrow – Tolterodine 2 Tablets (1mg and 2mg) are available in a PVC/ PVdC -Alublister pack

Each pack contains 14, 28, or 56 Tablets

Further Information

Preclinical Safety Data

In toxicity, genotoxicity, and carcinogenicity studies no clinically relevant effects have been observed, except those related to the pharmacological effect of the drug.

Reproduction studies have been performed in mice and rabbits.

In mice, there was no effect of tolterodine on fertility or reproductive function. Tolterodine produced embryo death and malformations at plasma exposures (Cmax or AUC) 20 or 7 times higher than those seen in treated humans.

In rabbits, no malformative effect was seen, but the studies were conducted at 20 or 3 times higher plasma exposure (Cmax or AUC) than those expected in treated humans.

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