

IRISH MEDICINES BOARD ACT 1995
MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998
(S.I. No.142 of 1998)

PPA1328/061/002

Case No: 2034068

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

B & S Healthcare

Unit 4, Bradfield Road, Ruislip, Middlesex, HA4 0NU, United Kingdom

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Detrusitol 2 mg Film-Coated Tablet

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **26/03/2007** until **28/09/2011**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Detrusitol 2 mg Film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains tolterodine tartrate 2mg corresponding to 1.37mg tolterodine.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Product imported from the Netherlands:

White, round and biconvex, tablet is engraved with arcs above and below the letters DT

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder syndrome.

4.2 Posology and method of administration

Adults (including the elderly):

The recommended dose is 2 mg twice daily except in patients with impaired liver function or severely impaired renal function (GFR \leq 30 ml/min) for whom the recommended dose is 1 mg twice daily (see section 4.4). In case of troublesome side effects the dose may be reduced from 2 mg to 1 mg twice daily.

The effect of treatment should be re-evaluated after 2-3 months (see section 5.1).

Children:

Safety and effectiveness in children have not yet been established. Therefore Detrusitol is not recommended for children, until more information is available.

4.3 Contraindications

Tolterodine is contra-indicated in patients with:

- urinary retention
- uncontrolled narrow angle glaucoma
- myasthenia gravis
- known hypersensitivity to tolterodine or excipients

- Severe ulcerative colitis
- toxic megacolon

4.4 Special warnings and precautions for use

Tolterodine shall be used with caution in patients with:

- significant bladder outlet obstruction at risk of urinary retention
- gastrointestinal obstructive disorders e.g. pyloric stenosis
- renal impairment (see section 4.2)
- hepatic disease. (see section 4.2 and 5.2)
- autonomic neuropathy
- hiatus hernia
- risk for decreased gastrointestinal motility

Multiple oral total daily doses of immediate release 4 mg (therapeutic) and 8 mg (supratherapeutic) tolterodine have been shown to prolong the QTc interval (see section 5.1). The clinical relevance of these findings is unclear and will depend on individual patient risk factors and susceptibilities present. Tolterodine should be used with caution in patients with risk factors for QT-prolongation including:

- Congenital or documented acquired QT prolongation
- Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia
- Bradycardia
- Relevant pre-existing cardiac diseases (i.e. cardiomyopathy, myocardial ischaemia, arrhythmia, congestive heart failure)
- Concomitant administration of drugs known to prolong QT-interval including Class IA (e.g. quinidine, procainamide) and Class III (e.g. amiodarone, sotalol) anti-arrhythmics.

This especially holds true when taking potent CYP3A4 inhibitors (see section 5.1). Concomitant treatment with potent CYP3A4 inhibitors should be avoided (see section 4.5, Interactions).

As with all treatments for symptoms of urgency and urge incontinence, organic reasons for urge and frequency should be considered before treatment.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant systemic medication with potent CYP3A4 inhibitors such as macrolide antibiotics (e.g. erythromycin and clarithromycin), antifungal agents (e.g. ketoconazole and itraconazole) and antiproteases is not recommended due to increased serum concentrations of tolterodine in poor CYP2D6 metabolisers with (subsequent) risk of overdosage (see section 4.4).

Concomitant medication with other drugs that possess antimuscarinic 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 effects of prokinetics like metoclopramide and cisapride may be decreased by tolterodine.

Concomitant treatment with fluoxetine (a potent CYP2D6 inhibitor) does not result in a clinically significant interaction since tolterodine and its CYP2D6-dependent metabolite, 5-hydroxymethyl tolterodine are equipotent.

Drug interaction studies have shown no interactions with warfarin or combined oral contraceptives (ethinylestradiol /levonorgestrel).

A clinical study has indicated that tolterodine is not a metabolic inhibitor of CYP2D6, 2C19, 3A4 or 1A2. Therefore an increase of plasma levels of drugs metabolised by the isoenzyme systems is not expected when dosed in combination with tolterodine.

4.6 Pregnancy and lactation

Pregnancy

There are no adequate data from the use of tolterodine in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Consequently, Detrusitol is not recommended during pregnancy.

Lactation

No data concerning the excretion of tolterodine into human milk are available. Tolterodine should be avoided during lactation.

4.7 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.

4.8 Undesirable effects

Due to the pharmacological effect of tolterodine it may cause mild to moderate antimuscarinic effects, like dryness of the mouth, dyspepsia and dry eyes.

The table below reflects the data obtained with Detrusitol in clinical trials and from postmarketing experience. The most commonly reported adverse reaction was dry mouth, which occurred in 35% of patients treated with Detrusitol tablets and in 10% of placebo treated patients.

	Common>1/100, <1/10	Uncommon >1/1000, <1/100	Rare >1/10000, <1/1000
Immune system disorders		Hypersensitivity not otherwise specified	
Psychiatric disorders	Nervousness	Confusion	Hallucinations
Nervous system disorders	Dizziness, somnolence, paresthesia		
Eye disorders	Dry eyes, abnormal vision including abnormal accomodation		
Cardiac disorders			Tachycardia
Gastrointestinal disorders	Dyspepsia, constipation, abdominal pain, flatulence, vomiting		
Skin and subcutaneous tissue disorders	Dry skin		
Renal and urinary disorders		Urinary retention	
General disorders	Fatigue, Headache, Chest pain,	Peripheral oedema	

Other adverse effects reported with the use of tolterodine are anaphylactoid reactions including angioedema (very rare) and cardiac failure (very rare). Palpitations and arrhythmia (rare) are known adverse effects for this drug class.

4.9 Overdose

The highest dose given to human volunteers of tolterodine L tartrate is 12.8 mg as single dose. The most severe adverse events observed were accommodation disturbances and micturition difficulties. In the event of tolterodine overdose, treat with gastric lavage and give activated charcoal. Treat symptoms as follows:

- Severe central anticholinergic effects (e.g. hallucinations, severe excitation): treat with physostigmine.
- Convulsions or pronounced excitation: treat with benzodiazepines.
- Respiratory insufficiency: treat with artificial respiration.
- Tachycardia: treat with beta-blockers.
- Urinary retention: treated with catheterization.
- Mydriasis: treat with pilocarpine eye drops and/or place patient in dark room

An increase in QT interval was observed at a total daily dose of 8 mg immediate release tolterodine (twice the recommended daily dose of the immediate release formulation and equivalent to three times the peak exposure of the prolonged release capsule formulation) administered over four days. In the event of tolterodine overdose, standard supportive measures for managing QT prolongation should be adopted.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urinary antispasmodics/
ATC code: G04B D07

Tolterodine is a competitive, specific muscarinic receptor antagonist with a selectivity for the urinary bladder over salivary glands in vivo. 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 Section 5.2).

Effect of the treatment can be expected within 4 weeks.

Effect of treatment with Detrusitol 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		
	Detrusitol 2 mg b.i.d.	Placebo	Statistical significance vs. placebo	Detrusitol 2 mg b.i.d.	Placebo	Statistical significance vs. placebo
Number of micturitions per 24 hours	-1.6	-0.9	*	-2.3	-1.4	**
	(-14%)	(-8%)		(-20%)	(-12%)	
	n=392	n=189		n=354	n=176	
Number of	-1.3	-1.0	n.s.	-1.6	-1.1	*

incontinence	(-38%)	(-26%)		(-47%)	(-32%)	
episodes per 24 hours	n=288	n=151		n=299	n=145	
Mean volume voided per micturition (ml)	+25	+12	***	+35	+10	***
	(+17%)	(+8%)		(+22%)	(+6%)	
	n=385	n=185		n=354	n=176	
Number of patients with no or minimal bladder problems after treatment (%)	16%	7%	**	19%	15%	n.s.
	n=394	n=190		n=356	N=177	

n.s.= not significant; *= $p \leq 0.05$; **= $p \leq 0.01$; ***= $p \leq 0.001$

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 randomised to receive either tolterodine or placebo. The study could not provide convincing evidence that tolterodine had effects over placebo in patients with sensory urgency.

The clinical effects of tolterodine on QT interval were studied in ECGs obtained from over 600 treated patients, including the elderly and patients with pre-existing cardiovascular disease. The changes in QT intervals did not significantly differ between placebo and treatment groups.

The effect of tolterodine on QT-prolongation was investigated further in 48 healthy male and female volunteers aged 18 – 55 years. Subjects were administered 2 mg BID and 4 mg BID tolterodine as the immediate release formulations. The results (Fridericia corrected) at peak tolterodine concentration (1 hour) showed mean QTc interval increases of 5.0 and 11.8 msec for tolterodine doses of 2 mg BID and 4 mg BID respectively and 19.8 msec for moxifloxacin (400 mg) which was used as an active, internal control. A pharmacokinetic/pharmacodynamic model estimated that QTc interval increases in poor metabolisers (devoid of CYP2D6) treated with tolterodine 2 mg BID are comparable to those observed in extensive metabolisers receiving 4 mg BID. At both doses of tolterodine, no subject, irrespective of their metabolic profile, exceeded 500 msec for absolute QTcF or 60 msec for change from baseline that are considered thresholds of particular concern. The 4 mg BID dose corresponds to a peak exposure (C_{max}) of three times that obtained with the highest therapeutic dose of Detrusitol SR capsules.

5.2 Pharmacokinetic properties

Pharmacokinetic characteristics specific for this formulation: 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 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 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 equipotent 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 orosomucoid. The unbound fractions are 3.7% and 36%, respectively. The volume of distribution of tolterodine is 113 L.

Elimination: 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. 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 and equipotent with tolterodine. 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.

The excretion of radioactivity after administration of [^{14}C]-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 liver function: About 2-fold higher exposure of unbound tolterodine and the 5-hydroxymethyl metabolite is found in subjects with liver cirrhosis (see section 4.2 and 4.4).

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 ≤ 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 is no data in mild to moderate renal impairment (see section 4.2 and 4.4).

5.3 Preclinical safety data

In toxicity, genotoxicity, carcinogenicity and safety pharmacology 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 (C_{max} 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 (C_{max} or AUC) than those expected in treated humans.

Tolterodine, as well as its active human metabolites prolong action potential duration (90% repolarisation) 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 – 26,1 times therapeutic levels). In dogs prolongation of the QT interval has been observed after

application of tolterodine and its human metabolites (3,1 – 61,0 times therapeutic levels). The clinical relevance of these findings is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, microcrystalline
Calcium hydrogen phosphate dihydrate
Sodium starch glycollate (type B)
Magnesium stearate
Colloidal anhydrous silica
Hypromellose
Cellulose, microcrystalline
Stearic acid
Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf-life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

PVC/PVDC and aluminium foil with a heat seal coating of PVDC. Tablets come in blister packs of 56 (4 x 14 tablets).

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 Parallel Product Authorisation Holder

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8 Parallel Product Authorisation Number

PPA 1328/61/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 29th September 2006

10 DATE OF REVISION OF THE TEXT

February 2007