Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

INCONEX XL 2 MG PROLONGED-RELEASE CAPSULES, HARD
BLERONE XL 2MG PROLONGED RELEASE CAPSULES
TOLTHEN XL 2 MG, PROLONGED-RELEASE CAPSULES, HARD
NEDITOL 2 MG, PROLONGED-RELEASE CAPSULES, HARD
INCONEX XL 4 MG PROLONGED-RELEASE CAPSULES, HARD
BLERONE XL 4MG PROLONGED RELEASE CAPSULES
TOLTHEN XL 4 MG PROLONGED-RELEASE CAPSULES, HARD
NEDITOL 4 MG, PROLONGED-RELEASE CAPSULES, HARD

(Tolterodine tartrate)

Procedure No: UK/H/2399, 2400, 4752 & 4753/001-2/DC

UK Licence No: PL 17277/0084-5, 0263-66 & 0271-2

PHARMATHEN SA.

LAY SUMMARY

On 15 March 2012, Belgium, Bulgaria, Cyprus, Czech Republic, Germany, Denmark, Estonia, Greece, Spain, Finland, Hungary, Ireland, Italy, Iceland, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Romania, Sweden, Slovakia and the UK agreed to grant Marketing Authorisations to Pharmathen SA for the medicinal products Inconex XL 2 mg and 4 mg Prolonged-release Capsules, Hard, Blerone XL 2mg and 4mg prolonged release capsules, Tolthen XL 2 mg and 4 mg Prolonged-release Capsules, Hard and Neditol XL 2 mg and 4 mg, prolonged-release capsules, hard (PL 17277/0084-5, 263-6 & 271-2; UK/H/2399-400 & 4752-3/001-2/DC). The licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, Marketing Authorisations were granted in the UK on 10 May 2012. These are Prescription-Only Medicines (POM).

These products will collectively be referred to as Inconex/Blerone/Tolthen/Neditol 2mg & 4 mg prolonged-release Capsules, Hard, throughout the remainder of this report.

Inconex/Blerone/Tolthen/Neditol 2mg & 4 mg prolonged-release Capsules, Hard, contain tolterodine as the active ingredient, which belongs to a group of medicines called antimuscarinics.

This medicine is used for the treatment of the symptoms of overactive bladder syndrome. If you have overactive bladder syndrome, you may find that you are unable to control urination, you need to rush to the toilet with no advance warning and/or go to the toilet frequently.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Inconex/Blerone/Tolthen/Neditol 2mg & 4 mg prolonged-release Capsules, Hard, outweigh the risks and Marketing Authorisations were granted.

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Module 1

Product Name	Inconex XL 2 mg and 4 mg Prolonged-release Capsules, Hard Blerone XL 2mg and 4mg prolonged release capsules Tolthen XL 2 mg and 4 mg Prolonged-release Capsules, Hard Neditol XL 2 mg and 4 mg, prolonged-release capsules, hard
Type of Application	Generic, Article 10.1 Hybrid, Article 10.3-applicable to PL 17277/0084-5; UK/H/2399/001-002 for CMS Malta only
Active Substances	Tolterodine tartrate
Form	Prolonged-release capsules, hard.
Strength	2 mg and 4 mg.
MA Holder	Pharmathen S.A., 6 Dervenakion str., Pallini Attki, 153 51 Greece
Reference Member State (RMS)	UK
Concerned Member State (CMS)	UK/H/2399/01/DC (PL 17277/0084): Belgium, Bulgaria, Germany, Denmark, Greece, Spain, Finland, Italy, Iceland, Luxembourg, Malta, Netherlands, Norway and Sweden. UK/H/2399/02/DC (PL 17277/0085): Belgium, Bulgaria, Germany, Denmark, Greece, Spain, Finland, Ireland, Iceland, Luxembourg, Malta, Netherlands, Norway and Sweden UK/H/4752/01-2/DC (PL 17277/0263-44): Czech Republic, Germany, Estonia, Spain, Hungary, Latvia, Lithuania, Romania and Slovakia UK/H/4753/01-2/DC (Pl 17277/0265-6): Belgium, Germany, Italy, Luxembourg, Netherlands and Poland. UK/H/2400/01-2/DC (PL 17277/0271-2): Cyprus, Germany, Greece, Spain, Iceland, Luxembourg and Poland.
Procedure Number	UK/H/2399-400 and 4752-3/001-2/DC
Timetable	Day 210– 15 March 2012.

Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Inconex XL 2 mg Prolonged-release Capsules, Hard
Blerone XL 2mg prolonged release capsules
Tolthen XL 2 mg, prolonged-release capsules, hard
Neditol XL 2 mg, prolonged-release capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One prolonged-release capsule, hard contains 2mg tolterodine tartrate, which is equivalent to 1.37 mg of tolterodine.

Each 2mg prolonged release capsule, hard contains 32.704-34.496 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release capsule, hard

Opaque green-opaque green size 1 hard gelatin capsules containing two white, round, biconvex coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Inconex/Blerone/Tolthen/Neditol XL is indicated in 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 4 mg once daily except in patients with impaired liver function or severely impaired renal function (GFR ≤ 30 ml/min) for whom the recommended dose is 2 mg once daily (see sections 4.4 and 5.2). In case of troublesome side-effects the dose may be reduced from 4 mg to 2 mg once daily.
The prolonged-release capsules, hard can be taken with or without food and must be swallowed whole.
The effect of treatment should be re-evaluated after 2-3 months (see section 5.1).
Paediatric population:
The efficacy of Inconex/Blerone/Tolthen/Neditol XL has not been demonstrated in children (see section 5.1). Therefore, Inconex/Blerone/Tolthen/Neditol XL is not recommended for children.

4.3 Contraindications

Tolterodine is contraindicated in patients with
- Hypersensitivity to the active substance or to any of the excipients
- Urinary retention
- Uncontrolled narrow angle glaucoma
- Myasthenia gravis
- 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 sections 4.2 and 5.2)
- Hepatic disease (see sections 4.2 and 5.2)
- Autonomic neuropathy
- Hiatus hernia
- Risk of 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.

This product contains approximately 67.2mg lactose (33.6mg glucose and 33.6mg galactose) per dose. This should be taken into account in patients with diabetes mellitus. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicinal product contains 0.00404 mmol (or 0.092988 mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant systemic medication with potent CYP3A4 inhibitors such as macrolide antibiotics (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 reduction in gastric motility caused by antimuscarinics may affect the absorbtion of other drugs.

The effect 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 (ethinyl estradiol/levonorgestrel).

A clinical study has indicated that tolterodine is not a metabolic inhibitor of CYP2D6, 2C19, 2C9, 3A4 or 1A2. Therefore, an increase of plasma levels of drugs metabolised by these isoenzymes is not expected when dosed in combination with tolterodine.

4.6 Fertility, 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, tolterodine is not recommended during pregnancy.

Lactation

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

Fertility
No data from fertility studies are available

4.7 Effects on ability to drive and use machines
Since this medicine 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.
Adverse reactions are listed below, by system organ class and by frequency. Frequencies are defined as: very common (≥1/10) common (≥1/100 to < 1/10), uncommon (≥1/1,000 to < 1/100), rare (≥1/10,000 to <1/1,000); very rare (< 1/10000) and not known (cannot be estimated from available data).
The table below reflects the data obtained with tolterodine in clinical trials and from post marketing experience. The most commonly reported adverse reaction was dry mouth, which occurred in 23.4 % of patients treated with tolterodine SR and in 7.7 % of placebo-treated patients.

Body System Class	**Very Common** (≥ 1/10)	**Common** (≥ 1/100 to <1/10)	**Uncommon** (≥ 1/1000 to <1/100)	**Not known** (cannot be estimated from the available data)
Infections and infestations		Sinusitis		
Immune system disorders			Hypersensitivity not otherwise specified	Anaphylactoid reactions
Psychiatric disorders			Nervousness	Confusion , hallucinations, disorientation
Nervous system disorders		Dizziness, somnolence, headache	Paresthesia, memory impairment	
Eye disorders		Dry eyes, abnormal vision (including abnormal accommodation)		
Ear and labyrinth disorders			Vertigo	
Cardiac disorders			Palpitations, cardiac failure, arrhythmia	Tachycardia
Vascular disorders				Flushing
Gastrointestinal disorders	Dry mouth	Dyspepsia, constipation, abdominal pain, flatulence, diarrhoea		Gastroesophageal reflux, vomiting
Skin and subcutaneous tissue disorders				Angioedema, dry skin
Renal and urinary		Dysuria	Urinary retention	

disorders				
General disorders and administration site disorders		Fatigue, peripheral oedema	Chest pain	

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.

Paediatric population
In two paediatric phase III randomised, placebo-controlled, double-blind studies conducted over 12 weeks where a total of 710 paediatric patients were recruited, the proportion of patients with urinary tract infections, diarrhoea and abnormal behaviour was higher in patients treated with tolterodine than placebo (urinary tract infection: tolterodine 6.8 %, placebo 3.6 %; diarrhoea: tolterodine 3.3 %, placebo 0.9 %; abnormal behaviour: tolterodine 1.6 %, placebo 0.4 %) (see section 5.1).

4.9 Overdose

The highest dose given to human volunteers of tolterodine tartrate is 12.8 mg as a single dose of the immediate release formulation. 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: treat with catheterisation
- 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: Genito urinary system and sex hormones
Pharmacotherapeutic sub-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).

The effect of the treatment can be expected within 4 weeks.

In the Phase III program, the primary endpoint was reduction of incontinence episodes per week and the secondary endpoints were reduction of micturitions per 24 hours and increase of mean volume voided per micturition. These parameters are presented in the following table.

The effect of treatment with tolterodine SR 4 mg once daily after 12 weeks, compared with placebo. Absolute change and percentage change relative to baseline. Treatment difference tolterodine vs. placebo: Least Squares estimated mean change and 95% confidence interval.

	tolterodine SR 4 mg once daily (n=507)	**Placebo (n=508)**	**Treatment difference vs. placebo: Mean change and 95% CI**	**Statistical significance vs. placebo (p-value)**
Number of incontinence episodes per week	-11.8 (-54%)	-6.9 (-28%)	-4.8 (-7.2; -2.5)*	<0.001
Number of micturitions per 24 hours	-1.8 (-13%)	-1.2 (-8%)	-0.6 (-1.0; -0.2)	0.005
Mean volume voided per micturition (ml)	+34 (+27%)	+14 (+12%)	+20 (14; 26)	<0.001

*) 97.5% confidence interval according to Bonferroni
After 12 weeks of treatment 23.8% (121/507) in the tolterodine SR 4 mg group and 15.7% (80/508) in the placebo group reported that they subjectively had no or minimal bladder problems.

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 and11.8 msec for tolterodine doses of 2 mg BID and 4 mg BID respectively and 19.3 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 (Cmax) of three times that obtained with the highest therapeutic dose of Tolterodine SR 4 mg capsules.

Paediatric population
The efficacy in the paediatric population has not been demonstrated. Two paediatric phase 3 randomised, placebo-controlled, double-blind 12 week studies were conducted using tolterodine extended release capsules. A total of 710 paediatric patients (486 on tolterodine and 224 on placebo) aged 5-10 years with urinary frequency and urge urinary incontinence were studied. No significant difference between the two groups was observed in either study with regard to change from baseline in total number of incontinence episodes/week (see section 4.8).

5.2 Pharmacokinetic properties

Pharmacokinetic characteristics specific for this formulation:
Tolterodine prolonged-release capsules, hard give a slower absorption of tolterodine than the immediate-release tablets do. As a result, the maximum serum concentrations are observed 4 (2-6) hours after administration of the capsules. The apparent half-life for tolterodine given as the capsule is about 6 hours in extensive and about 10 hours in poor metabolisers (devoid of CYP2D6). Steady state concentrations are reached within 4 days after administration of the capsules.

There is no effect of food on the bioavailability of the capsules.

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 [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:

Patients with liver impairement:
About 2-fold higher exposure of unbound tolterodine and the 5-hydroxymethyl metabolite is found in subjects with liver cirrhosis (see sections 4.2 and 4.4).

Patients with renal impairement:
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).

Paediatric population
The exposure of the active moiety per mg dose is similar in adults and adolescents. The mean exposure of the active moiety per mg dose is approximately two-fold higher in children between 5-10 years than in adults (see sections 4.2 and 5.1).

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.

Reprotoxicity 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 malformations were observed at plasma exposures (Cmax or AUC) that were 20 or 3 times higher than those expected in 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

Lactose monohydrate
Cellulose microcrystalline
Poly (vinyl acetate)
Povidone
Silica
Sodium laurylsulfate
Docusate Sodium
Magnesium stearate (E470b)
Hydroxypropylmethylcellulose

Capsule composition:
- Indigo carmine (E132)
- Quinoline yellow (E104)
- Titanium dioxide (E171)
- Gelatin

Coating consisting of:
- Ethylcellulose
- Triethyl citrate
- Methacrylic acid - ethyl acrylate copolymer
- 1,2-Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

HDPE bottle: Shelf life after first opening is 200 days

6.4 Special precautions for storage

Do not store above 25°C

6.5 Nature and contents of container

A cardboard box containing the appropriate number of blisters of transparent PVC/PE/PVDC Aluminium foil and an instruction leaflet.

For PL 17277/0084:
Blister packs containing: 7, 14, 28, 30, 49, 50, 56, 80, 84, 90, 98, 100, 112, 160, 280, 320 prolonged-release hard capsules.

For PL 17277/0263:
Blister packs containing: 14, 28, 84 prolonged-release hard capsules

For PL 17277/0265 & 0271:
Blister packs containing: 14, 28, 56, 84 prolonged-release hard capsules

For all PL numbers:
A cardboard box containing a white opaque HDPE bottle containing the appropriate number of capsules with screw cap and an instruction leaflet.
Pack sizes of: 30, 100 and 200 capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Pharmathen S.A
6, Dervenakion str.,
153 51 Pallini
Attiki, Greece

8 MARKETING AUTHORISATION NUMBER(S)

PL 17277/0084
PL 17277/0263
PL 17277/0265
PL 17277/0271

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10/05/2012

10 DATE OF REVISION OF THE TEXT

10/05/2012

1 NAME OF THE MEDICINAL PRODUCT

Inconex XL 4 mg Prolonged-release Capsules, Hard
Blerone XL 4 mg prolonged release capsules
Tolthen XL 4 mg, prolonged-release capsules, hard
Neditol XL 4 mg, prolonged-release capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One prolonged-release capsule, hard contains 4mg tolterodine tartrate, which is equivalent to 2.74 mg of tolterodine.

Each 4mg prolonged release capsule, hard contains 65.408-68.992 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release capsule, hard

Light blue opaque-light blue opaque size 1 hard gelatin capsules containing four white, round, biconvex coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Inconex/Blerone/Tolthen/Neditol XL is indicated in 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 4 mg once daily except in patients with impaired liver function or severely impaired renal function (GFR ≤ 30 ml/min) for whom the recommended dose is 2 mg once daily (see sections 4.4 and 5.2). In case of troublesome side-effects the dose may be reduced from 4 mg to 2 mg once daily.

The prolonged-release capsules, hard can be taken with or without food and must be swallowed whole.

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

Paediatric population:
The efficacy of Inconex/Blerone/Tolthen/Neditol XL has not been demonstrated in children (see section 5.1). Therefore, Inconex/Blerone/Tolthen/Neditol XL is not recommended for children.

4.3 Contraindications

Tolterodine is contraindicated in patients with
- Hypersensitivity to the active substance or to any of the excipients
- Urinary retention
- Uncontrolled narrow angle glaucoma
- Myasthenia gravis
- 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 sections 4.2 and 5.2)
- Hepatic disease (see sections 4.2 and 5.2)
- Autonomic neuropathy
- Hiatus hernia
- Risk of 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.

This product contains approximately 67.2mg lactose (33.6mg glucose and 33.6mg galactose) per dose. This should be taken into account in patients with diabetes mellitus. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicinal product contains 0.00404 mmol (or 0.092988 mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant systemic medication with potent CYP3A4 inhibitors such as macrolide antibiotics (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 reduction in gastric motility caused by antimuscarinics may affect the absorbtion of other drugs.

The effect 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 (ethinyl estradiol/levonorgestrel).

A clinical study has indicated that tolterodine is not a metabolic inhibitor of CYP2D6, 2C19, 2C9, 3A4 or 1A2. Therefore, an increase of plasma levels of drugs metabolised by these isoenzymes is not expected when dosed in combination with tolterodine.

4.6 Fertility, 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, tolterodine is not recommended during pregnancy.

Lactation

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

Fertility
No data from fertility studies are available

4.7 Effects on ability to drive and use machines
Since this medicine 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.

Adverse reactions are listed below, by system organ class and by frequency. Frequencies are defined as: very common (≥1/10) common (≥1/100 to < 1/10), uncommon (≥1/1,000 to < 1/100), rare (≥1/10,000 to <1/1,000); very rare (< 1/10000) and not known (cannot be estimated from available data).
The table below reflects the data obtained with tolterodine in clinical trials and from post marketing experience. The most commonly reported adverse reaction was dry mouth, which occurred in 23.4 % of patients treated with tolterodine SR and in 7.7 % of placebo-treated patients.

Body System Class	**Very Common** (≥ 1/10)	**Common** (≥ 1/100 to <1/10)	**Uncommon** (≥ 1/1000 to <1/100)	**Not known** (cannot be estimated from the available data)
Infections and infestations		Sinusitis		
Immune system disorders			Hypersensitivity not otherwise specified	Anaphylactoid reactions
Psychiatric disorders			Nervousness	Confusion , hallucinations, disorientation
Nervous system disorders		Dizziness, somnolence, headache	Paresthesia, memory impairment	
Eye disorders		Dry eyes, abnormal vision (including abnormal accommodation)		
Ear and labyrinth disorders			Vertigo	
Cardiac disorders			Palpitations, cardiac failure, arrhythmia	Tachycardia
Vascular disorders				Flushing
Gastrointestinal disorders	Dry mouth	Dyspepsia, constipation, abdominal pain, flatulence, diarrhoea		Gastroesophageal reflux, vomiting
Skin and subcutaneous tissue disorders				Angioedema, dry skin

Renal and urinary disorders		Dysuria	Urinary retention	
General disorders and administration site disorders		Fatigue, peripheral oedema	Chest pain	

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.

Paediatric population
In two paediatric phase III randomised, placebo-controlled, double-blind studies conducted over 12 weeks where a total of 710 paediatric patients were recruited, the proportion of patients with urinary tract infections, diarrhoea and abnormal behaviour was higher in patients treated with tolterodine than placebo (urinary tract infection: tolterodine 6.8 %, placebo 3.6 %; diarrhoea: tolterodine 3.3 %, placebo 0.9 %; abnormal behaviour: tolterodine 1.6 %, placebo 0.4 %) (see section 5.1).

4.9 Overdose

The highest dose given to human volunteers of tolterodine tartrate is 12.8 mg as a single dose of the immediate release formulation. 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: treat with catheterisation
- 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: Genito urinary system and sex hormones
Pharmacotherapeutic sub-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).

The effect of the treatment can be expected within 4 weeks.

In the Phase III program, the primary endpoint was reduction of incontinence episodes per week and the secondary endpoints were reduction of micturitions per 24 hours and increase of mean volume voided per micturition. These parameters are presented in the following table.

The effect of treatment with tolterodine SR 4 mg once daily after 12 weeks, compared with placebo. Absolute change and percentage change relative to baseline. Treatment difference tolterodine vs. placebo: Least Squares estimated mean change and 95% confidence interval.

	tolterodine SR 4 mg once daily (n=507)	**Placebo (n=508)**	**Treatment difference vs. placebo: Mean change and 95% CI**	**Statistical significance vs. placebo (p-value)**
Number of incontinence episodes per week	-11.8 (-54%)	-6.9 (-28%)	-4.8 (-7.2; -2.5)*	<0.001
Number of micturitions per 24 hours	-1.8 (-13%)	-1.2 (-8%)	-0.6 (-1.0; -0.2)	0.005
Mean volume voided per micturition (ml)	+34 (+27%)	+14 (+12%)	+20 (14; 26)	<0.001

*) 97.5% confidence interval according to Bonferroni
After 12 weeks of treatment 23.8% (121/507) in the tolterodine SR 4 mg group and 15.7% (80/508) in the placebo group reported that they subjectively had no or minimal bladder problems.

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 and11.8 msec for tolterodine doses of 2 mg BID and 4 mg BID respectively and 19.3 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 (Cmax) of three times that obtained with the highest therapeutic dose of Tolterodine SR 4 mg capsules.

Paediatric population
The efficacy in the paediatric population has not been demonstrated. Two paediatric phase 3 randomised, placebo-controlled, double-blind 12 week studies were conducted using tolterodine extended release capsules. A total of 710 paediatric patients (486 on tolterodine and 224 on placebo) aged 5-10 years with urinary frequency and urge urinary incontinence were studied. No significant difference between the two groups was observed in either study with regard to change from baseline in total number of incontinence episodes/week (see section 4.8).

5.2 Pharmacokinetic properties

Pharmacokinetic characteristics specific for this formulation:
Tolterodine prolonged-release capsules, hard give a slower absorption of tolterodine than the immediate-release tablets do. As a result, the maximum serum concentrations are observed 4 (2-6) hours after administration of the capsules. The apparent half-life for tolterodine given as the capsule is about 6 hours in extensive and about 10 hours in poor metabolisers (devoid of CYP2D6). Steady state concentrations are reached within 4 days after administration of the capsules.

There is no effect of food on the bioavailability of the capsules.

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 [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:

Patients with liver impairement:
About 2-fold higher exposure of unbound tolterodine and the 5-hydroxymethyl metabolite is found in subjects with liver cirrhosis (see sections 4.2 and 4.4).

Patients with renal impairement:
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).

Paediatric population
The exposure of the active moiety per mg dose is similar in adults and adolescents. The mean exposure of the active moiety per mg dose is approximately two-fold higher in children between 5-10 years than in adults (see sections 4.2 and 5.1).

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.

Reprotoxicity 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 malformations were observed at plasma exposures (Cmax or AUC) that were 20 or 3 times higher than those expected in 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

Lactose monohydrate
Cellulose microcrystalline
Poly (vinyl acetate)
Povidone
Silica
Sodium laurylsulfate
Docusate Sodium
Magnesium stearate (E470b)
Hydroxypropylmethylcellulose

Capsule composition:
- Indigo carmine (E132)
- Quinoline yellow (E104)
- Titanium dioxide (E171)
- Gelatin

Coating consisting of:
- Ethylcellulose
- Triethyl citrate
- Methacrylic acid - ethyl acrylate copolymer
- 1,2-Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

HDPE bottle: Shelf life after first opening is 200 days

6.4 Special precautions for storage

Do not store above 25°C

6.5 Nature and contents of container

A cardboard box containing the appropriate number of blisters of transparent PVC/PE/PVDC Aluminium foil and an instruction leaflet.

For PL 17277/0085 & 0266:
Blister packs containing: 7, 14, 28, 30, 49, 50, 56, 80, 84, 90, 98, 100, 112, 160, 280, 320 prolonged-release hard capsules.

For PL 17277/0264:
Blister packs containing: 7, 14, 28, 49, 84, 98 prolonged-release hard capsules

For PL 17277/0272:
Blister packs containing: 7, 14, 28, 49, 56, 84, 98 prolonged-release hard capsules

For all PL numbers:
A cardboard box containing a white opaque HDPE bottle containing the appropriate number of capsules with screw cap and an instruction leaflet.
Pack sizes of: 30, 100 and 200 capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Pharmathen S.A
6, Dervenakion str.,
153 51 Pallini
Attiki, Greece

8 MARKETING AUTHORISATION NUMBER(S)

PL 17277/0085
PL 17277/0264
PL 17277/0266
PL 17277/0272

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10/05/2012

10 DATE OF REVISION OF THE TEXT

10/05/2012

Module 3

The following text is the approved Patient Information Leaflet (PIL) text as agreed during the decentralised procedure. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the PIL mock-up has been obtained.

PACKAGE LEAFLET: INFORMATION FOR THE USER

[Tolterodine] SR 2 mg prolonged-release capsules, hard
[Tolterodine] SR 4 mg prolonged-release capsules, hard

Tolterodine tartrate

Read all of this leaflet carefully before you start using this medicine:
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What [Tolterodine] SR is and what it is used for

The active substance in [Tolterodine] is tolterodine. Tolterodine belongs to a class of medicinal products called antimuscarinics.

[Tolterodine] is used for the treatment of the symptoms of overactive bladder syndrome. If you have overactive bladder syndrome, you may find that:
- you are unable to control urination
- you need to rush to the toilet with no advance warning and/or go to the toilet frequently

2. Before you take [Tolterodine] SR

Do not take [Tolterodine] SR if you:
- are allergic (hypersensitive) to tolterodine or any of the other ingredients in [Tolterodine] (see section 6 for a list of the ingredients)
- are unable to pass urine from the bladder (urinary retention)
- have an uncontrolled narrow-angle glaucoma (high pressure in the eyes with loss of eyesight that is not being adequately treated)
- suffer from myasthenia gravis (excessive weakness of the muscles)
- suffer from severe ulcerative colitis (ulceration and inflammation of the colon)
- suffer from a toxic megacolon (acute dilatation of the colon).

Take special care with [Tolterodine] SR:

- If you have difficulties in passing urine and/or a poor stream of urine.
- If you have a gastro-intestinal disease that affects the passage and/or digestion of food.
- If you suffer from kidney problems (renal insufficiency).
- If you have a liver condition.
- If you suffer from neurological disorders that affect your blood pressure, bowel or sexual function (any neuropathy of the autonomic nervous system).
- If you have a hiatus hernia (herniation of an abdominal organ).
- If you ever experience decreased bowel movements or suffer from severe constipation (decreased gastro-intestinal motility).
- If you have a heart condition such as:
  - an abnormal heart tracing (ECG)
  - a slow heart rate (bradycardia)
  - relevant pre-existing cardiac diseases such as: cardiomyopathy (weak heart muscle), myocardial ischaemia (reduced blood flow to the heart), arrhythmia (irregular heartbeat) and heart failure
- If you have abnormally low levels of potassium (hypokalaemia), calcium (hypocalcaemia) or magnesium (hypomagnesaemia) in your blood.

Contains approximately 67.2mg lactose (33.6mg glucose and 33.6mg galactose) per dose. This should be taken into account in patients with diabetes mellitus.

This medicinal product contains 0.00404 mmol (or 0.092988 mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

Talk to your doctor or pharmacist before starting your treatment with [Tolterodine] if you think any of these might apply to you.

Taking other medicines

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Tolterodine, the active substance of [Tolterodine], may interact with other medicinal products.

It is not recommended to use tolterodine in combination with:

- some antibiotics (containing e.g. erythromycin, clarithromycin)
- medicinal products used for the treatment of fungal infections (containing e.g. ketoconazole, itraconazole)
- medicinal products used for the treatment of HIV

[Tolterodine] should be used with caution when taken in combination with:

- medicines that affect the passage of food (containing e.g. metoclopramide and cisapride)
- medicines for the treatment of irregular heartbeat (containing e.g. amiodarone, sotalol, quinidine, procainamide other medicines with a similar mode of action to [Tolterodine] (antimuscarinic properties) or medicines with an opposite mode of action to [Tolterodine] (cholinergic properties). The reduction in gastric motility caused by antimuscarinics may affect the absorption of other drugs. Ask your doctor if you are unsure.

Taking [Tolterodine] SR with food and drink

[Tolterodine] can be taken before, after or during a meal.

Pregnancy and breast-feeding

Pregnancy
You should not use [Tolterodine] when you are pregnant. Tell your doctor immediately if you are pregnant, think you are pregnant or are planning to become pregnant.

Breast-feeding
It is not known if tolterodine, the active substance of [Tolterodine], is excreted in the mother's breast milk. Breast-feeding is not recommended during administration of [Tolterodine].

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

[Tolterodine] may make you feel dizzy, tired or affect your sight. If you experience any of these affects then you should not drive your car or operate heavy machinery.

3. How to take [Tolterodine] SR

Dosage:
Always take [Tolterodine] exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The prolonged-release hard capsules are for oral use and should be swallowed whole.
Do not chew the capsules.

Adults:
The usual dose is one 4 mg prolonged-release hard capsule daily.

Patients with liver or kidney problems:
In patients with liver or kidney problems your doctor may reduce your dose to 2 mg [Tolterodine] daily.

Children:
[Tolterodine] is not recommended for children.

If you have taken more [Tolterodine] SR than you should:
If you or somebody else takes too many prolonged-release capsules, contact your doctor or pharmacist immediately. Symptoms in case of overdose include hallucinations, excitation, a heartbeat faster than usual, dilation of the pupil and inability to urinate or breathe normally.

If you forget to take [Tolterodine] SR:
If you forget to take a dose at the usual time, take it as soon as you remember unless it is almost time for your next dose. In that case, omit the forgotten dose and follow the normal dose schedule.
Do not take a double dose to make up for a forgotten one.

If you stop taking [Tolterodine] SR
Your doctor will tell you how long your treatment with [Tolterodine] will last. Do not stop treatment early because you do not see an immediate effect. Your bladder will need some time to adapt. Finish the course of prolonged-release capsules prescribed by your doctor. If you have not noticed any effect by then, talk to your doctor.

The benefit of the treatment should be re-evaluated after 2 or 3 months. Always consult your doctor if you are thinking of stopping the treatment.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, [Tolterodine] can cause side effects, although not everybody gets them.

You should see your doctor immediately or go to the casualty department if you experience symptoms of angioedema, such as:

- swollen face, tongue or pharynx
- difficulty to swallow
- hives and difficulty in breathing

You should also seek medical attention if you experience a hypersensitivity reaction (for example itching, rash, hives, difficulty breathing). This occurs uncommonly (occurs in less than 1 in 100 patients).

Tell your doctor immediately or go to the casualty department if you notice any of the following:

- chest pain, difficulty breathing or getting tired easily (even at rest), difficulty breathing at night, swelling of the legs.

These may be symptoms of heart failure. This occurs uncommonly (occurs in less than 1 in 100 patients).

The following side effects have been observed during treatment with [Tolterodine] with the following frequencies.

Very common side effects (occurs in more than 1 in 10 patients) are:

- Dry mouth

Common side effects (occurs in less than 1 in 10 patients) are:

- Sinusitis
- Sleepiness
- Dry eyes
- Difficulty with digestion (dyspepsia)
- Abdominal pain
- Painful or difficult urination
- Extra fluid in the body causing swelling (e.g. in the ankles)
- Dizziness
- Headache
- Blurred vision
- Constipation
- excessive amounts of air or gases in the stomach or the intestine
- Diarrhoea
- Tiredness

Uncommon side effects (occurs in less than 1 in 100 patients) are:

- Allergic reactions
- Nervousness
- Palpitations
- Inability to empty the bladder
- Vertigo
- Heart failure
- Irregular heartbeat
- Chest pain
- Sensation of pins and needles in the fingers and toes
- Memory impairment

Additional reactions reported include severe allergic reactions, confusion, hallucinations, increased heart rate, flushed skin, heart burn, vomiting, angioedema, dry skin, and disorientation. There have also been reports of worsening symptoms of dementia in patients being treated for dementia.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet,

please tell your doctor or pharmacist.

5. How to store [TOLTERODINE] SR

Keep [Tolterodine] out of the reach and sight of children.

Do not use [Tolterodine] after the expiry date which is stated on the label/carton. The expiry date refers to the last day of that month.

Do not store above 25°C

HDPE bottle: Shelf life after first opening is 200 days

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further information

What [Tolterodine] SR contains

The active substance in [Tolterodine] 2 mg prolonged-release capsules, hard is 2 mg of tolterodine tartrate, equivalent to 1.37 mg of tolterodine.

The active substance in [Tolterodine] 4 mg prolonged-release capsules, hard is 4 mg of tolterodine tartrate, equivalent to 2.74 mg of tolterodine.

The other ingredients are:
Lactose monohydrate, cellulose microcrystalline, poly(vinyl acetate), povidone, sodium docusate, magnesium stearate, hydroxypropylmethylcellulose
Capsule composition: indigo carmine (E132), quinoline yellow (only in 2 mg) (E104), titanium dioxide (E171), gelatin
Inner tablet coating: ethylcellulose, triethyl citrate, methacrylic acid - ethyl acrylate copolymer, 1,2-Propylene glycol

What [Tolterodine] SR looks like and contents of the pack

[Tolterodine] is a hard prolonged-release capsule designed for once daily dosing.
[Tolterodine] 2 mg prolonged-release hard capsules are green-opaque.
[Tolterodine] 4 mg prolonged-release hard capsules are blue-opaque-light blue opaque.

[Tolterodine] 2 mg prolonged-release hard capsules are available in the following pack sizes:

UK/H/2399/01/DC
Blister packs containing: 7, 14, 28, 30, 49, 50, 56, 80, 84, 90, 98, 100, 112, 160, 280, 320 prolonged-release hard capsules

UK/H/4752, 4753/01/DC
Blister packs containing: 14, 28, 84 prolonged-release hard capsules

UK/H/2400/01/DC
Blister packs containing: 14, 28, 56, 84 prolonged-release hard capsules

[Tolterodine] 4 mg prolonged-release hard capsules are available in the following pack sizes:

UK/H/2399/02/DC

Blister packs containing: 7, 14, 28, 30, 49, 50, 56, 80, 84, 90, 98, 100, 112, 160, 280, 320 prolonged-release hard capsules

UK/H/4752, 4753/02/DC
Blister packs containing: 7, 14, 28, 49, 84, 98 prolonged-release hard capsules

UK/H/2400/02/DC
Blister packs containing: 7, 14, 28, 49, 56, 84, 98 prolonged-release hard capsules

For all procedures 2mg and 4mg:
HPDE bottles containing: 30, 100 and 200 prolonged-release hard capsules.
Not all pack sizes may be marketed.

Marketing authorisation holder and manufacturer

Marketing authorisation holder:
<to be completed nationally>

Manufacturer:
<to be completed nationally>

This medicinal product is authorized in the Member States of the EEA under the following names:

UK/H/2399/001-002/DC

UK	Danadine XL 2mg, 4mg prolonged release capsules, hard
BE	Tolterodin Sandoz 2mg, 4mg, harde capsules met verlengde afgifte
BG:	Tolterodine Sandoz
DE:	Tolterodin HEXAL® retard 2mg/ 4 mg
DK:	Tolterodine Sandoz
ES:	Tolterodina Neo Sandoz 2mg/4 mg cápsulas de liberación prolongada EFG
EL:	Tolterodine Sandoz
FI:	Tolterodine Sandoz
IE:	Toltex2mg/4mg Prolonged-Release Capsules, Hard
IS:	Tolterodine Sandoz
LU:	Tolterodin Sandoz 2mg/ 4mg, gelules a liberation prolongee
MT:	Danadine XL 2mg/4mg prolonged release capsules, hard
NL:	Tolterodinetartraat Sandoz retard 2mg/4 mg, harde capsules met verlengde afgifte
NO:	Tolterodine Sandoz
SE:	Tolterodine Sandoz

UK/H/2400/001-002/DC

UK	Neditol 2mg, 4mg prolonged release capsules
CY	Trudine 2mg, 4mg prolonged release capsules
DE	Neditol 2mg, 4mg prolonged release capsules
ES	Tolterodina Edigen 2mg, 4mg cápsulas duras de liberación prolongada EFG
IS	Tolterodine Portfarma 2mg, 4mg prolonged release capsules
LU	Tolterodine Portfarma 2mg, 4mg prolonged release capsules
PL	Tolzurin
EL	Toldesor 2mg, 4mg prolonged release capsules

UK/H/4752/001-002/DC

UK	Blerone 2mg, 4mg prolonged release capsules
CZ	Uroflow UNO2 mg, 4mg tvrdé tobolky s prodlouženým uvolňováním
EE	Uroflow 2 mg, 4mg

HU	Uroflow SR 2mg, 4mg módosított hatóanyagleadású kapszula
LT	Uroflow 2mg, 4mg pailginto atpalaidavimo kietos kapsulės
LV	Uroflow 2mg, 4mg ilgstošās darbības cietās kapsulas
RO	Uroflow SR 2 mg, mg capsule cu eliberare prelungită
SK	Uroflow SR 2mg, 4mg kapsuly s predĺženým uvoľňovaním

UK/H/4753/001-002/DC

UK	Titlodine 2mg, 4mg prolonged release capsules
DE	Titlodine 2mg, 4mg prolonged release capsules
PL	Titlodine 2mg, 4mg prolonged release capsules
IT	Tolterodina Doc
BE	Urolina 2mg, 4mg prolonged release capsules
LU	Urolina 2mg, 4mg prolonged release capsules
NL	Uroline 2mg, 4mg prolonged release capsules

This leaflet was last approved in {MM/YYYY}

Module 4
Labelling

The following text is the approved labelling text as agreed during the decentralised procedure. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the labelling mock-ups has been obtained.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER PACKING/ BLISTER

1. NAME OF THE MEDICINAL PRODUCT

[Tolterodine] SR 2 mg prolonged-release capsules, hard
Tolterodine tartrate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 2 mg of tolterodine tartrate, which is equivalent to 1,37 mg of tolterodine.

3. LIST OF EXCIPIENTS

Also contains lactose and sodium

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release hard capsules

Pack sizes:

UK/H/2399/01/DC
7 prolonged-release capsules, hard
14 prolonged-release capsules, hard
28 prolonged-release capsules, hard
30 prolonged-release capsules, hard
49 prolonged-release capsules, hard
50 prolonged-release capsules, hard
56 prolonged-release capsules, hard
80 prolonged-release capsules, hard
84 prolonged-release capsules, hard
90 prolonged-release capsules, hard
98 prolonged-release capsules, hard
100 prolonged-release capsules, hard
112 prolonged-release capsules, hard
160 prolonged-release capsules, hard
280 prolonged-release capsules, hard
320 prolonged-release capsules, hard

UK/H/4752, 4753/01/DC
14 prolonged-release capsules, hard
28 prolonged-release capsules, hard
84 prolonged-release capsules, hard

UK/H/2400/01/DC
14 prolonged-release capsules, hard
28 prolonged-release capsules, hard
56 prolonged-release capsules, hard
84 prolonged-release capsules, hard

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Shelf life: 24 months

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

12. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

<To be completed nationally>

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[Tolterodine] SR 2 mg capsules

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

[Tolterodine] SR 2 mg prolonged-release capsules, hard
Tolterodine Tartrate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

3. EXPIRY DATE

EXP
Shelf life: 24 months

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER PACKING/ BOTTLE PACK

1. NAME OF THE MEDICINAL PRODUCT

[Tolterodine] SR 2 mg prolonged-release capsules, hard
Tolterodine tartrate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 2 mg of tolterodine tartrate, which is equivalent to 1,37mg of tolterodine

3. LIST OF EXCIPIENTS

Also contains lactose and sodium

4. PHARMACEUTICAL FORM AND CONTENTS

30 prolonged-release capsules, hard
100 prolonged-release capsules, hard
200 prolonged-release capsules, hard

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
HDPE bottle: Shelf life after first opening is 200 days

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

12. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

<To be completed nationally>

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[Tolterodine] SR 2 mg capsules

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

[Tolterodine] SR 2 mg prolonged-release capsules, hard
Tolterodine tartrate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 2 mg of tolterodine tartrate, which is equivalent to 1,37mg of tolterodine

3. LIST OF EXCIPIENTS

Also contains lactose and sodium

4. PHARMACEUTICAL FORM AND CONTENTS

30 prolonged-release capsules, hard
100 prolonged-release capsules, hard
200 prolonged-release capsules, hard

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Shelf life after first opening is 200 days

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

12. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

<To be completed nationally>

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[Tolterodine] SR 2 mg capsules

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER PACKING/ BLISTER

1. NAME OF THE MEDICINAL PRODUCT

[Tolterodine] SR 4 mg prolonged-release capsules, hard
Tolterodine tartrate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 4 mg of tolterodine tartrate which is equivalent to 2,74mg of tolterodine.

3. LIST OF EXCIPIENTS

Also contains lactose and sodium

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release hard capsules

Pack sizes:

UK/H/2399/01/DC
7 prolonged-release capsules, hard
14 prolonged-release capsules, hard
28 prolonged-release capsules, hard
30 prolonged-release capsules, hard
49 prolonged-release capsules, hard
50 prolonged-release capsules, hard
56 prolonged-release capsules, hard
80 prolonged-release capsules, hard
84 prolonged-release capsules, hard
90 prolonged-release capsules, hard
98 prolonged-release capsules, hard
100 prolonged-release capsules, hard
112 prolonged-release capsules, hard
160 prolonged-release capsules, hard
280 prolonged-release capsules, hard
320 prolonged-release capsules, hard

UK/H/4752, 4753/02/DC
7 prolonged-release capsules, hard
14 prolonged-release capsules, hard
28 prolonged-release capsules, hard
49 prolonged-release capsules, hard
84 prolonged-release capsules, hard
98 prolonged-release capsules, hard

UK/H/2400/02/DC
7 prolonged-release capsules, hard
14 prolonged-release capsules, hard
28 prolonged-release capsules, hard

49 prolonged-release capsules, hard
56 prolonged-release capsules, hard
84 prolonged-release capsules, hard
98 prolonged-release capsules, hard

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Shelf life: 24 months

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

12. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

<To be completed nationally>

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[Tolterodine] SR 4 mg capsules

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

[Tolterodine] SR 4 mg prolonged-release capsules, hard
Tolterodine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

3. EXPIRY DATE

EXP
Shelf life: 24 months

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER PACKING/ BOTTLE PACK

1. NAME OF THE MEDICINAL PRODUCT

[Tolterodine] SR 4 mg prolonged-release capsules, hard
Tolterodine tartrate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 4 mg of tolterodine tartrate, which is equivalent to 2,74mg of tolerodine

3. LIST OF EXCIPIENTS

Also contains lactose and sodium

4. PHARMACEUTICAL FORM AND CONTENTS

30 prolonged-release capsules, hard
100 prolonged-release capsules, hard
200 prolonged-release capsules, hard

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
HDPE bottle: Shelf life after first opening is 200 days

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

12. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

<To be completed nationally>

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[Tolterodine] SR 4 mg capsules

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

[Tolterodine] SR 4 mg prolonged-release capsules, hard
Tolterodine tartrate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 4 mg of tolterodine tartrate, which is equivalent to 2,74mg of tolterodine

3. LIST OF EXCIPIENTS

Also contains lactose and sodium

4. PHARMACEUTICAL FORM AND CONTENTS

30 prolonged-release capsules, hard
100 prolonged-release capsules, hard
200 prolonged-release capsules, hard

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

12. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

<To be completed nationally>

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[Tolterodine] SR 4 mg capsules

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for Inconex/Blerone/Tolthen/Neditol 2mg & 4 mg prolonged-release Capsules, Hard (PL 17277/0084-5, 263-6 & 271-2; UK/H/2399-400 & 4752-3/001-2/DC) could be approved. These applications were submitted via the decentralised procedure, with the UK as Reference Member State (RMS) and Belgium, Bulgaria, Cyprus, Czech Republic, Germany, Denmark, Estonia, Greece, Spain, Finland, Hungary, Ireland, Italy, Iceland, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Romania, Sweden and Slovakia as Concerned Member State (CMS). These products are prescription-only medicines (POM).

Inconex/Blerone/Tolthen/Neditol 2mg & 4 mg prolonged-release Capsules, Hard, are indicated in symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder syndrome.

These are abridged applications submitted under Article 10(1) and 10(3) [applicable to PL 17277/0084-5; UK/H/2399/001-002 for CMS Malta only] of Directive 2001/83/EC as amended, referring to Detrusitol 1mg film-coated tablets (Pfizer AB, Sweden), which was first authorised in Sweden on 05 September 1997. The legal basis for the submission in CMS Malta is 10(3) a so called hybrid application, as this submission concerns a change in pharmaceutical form and change in strength. The cross-reference products in the UK are Detrusitol XL 2.0mg and 4.0mg prolonged-release capsules, Hard, authorised to Pharmacia Limited in August 2001. The product used in the bioequivalence studies was Detrusitol 4mg retard hard capsules (Pharmacia GmbH, Germany) taken from the German market. It has been confirmed that this can be considered equivalent to the same product from the UK market.

Tolterodine is a competitive, specific muscarinic receptor antagonist with 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 of SmPC).

No new non-clinical studies were conducted, which is acceptable given that the products are intended to be generic versions, cross-referring to products that have been licensed for over 10 years.

Three bioequivalence studies (two single-dose studies and one steady state) were submitted to support these applications, comparing the test product Tolterodine SR 4mg capsules (Pharmathen S.A) with the reference product Detrusitol 4mg retard hard capsules (Pharmacia GmbH, Germany).

With the exception of the bioequivalence studies, no new clinical studies were conducted, which is acceptable given that the applications were for products that are intended to be generic versions cross-referring to products that have been licensed for over 10 years. The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

The RMS and CMS considered that the applications could be approved with the end of procedure (Day 210) on 15 March 2012. After a subsequent national phase, the licences were granted in the UK on 10 May 2012.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Inconex XL 2 mg and 4 mg Prolonged-release Capsules, Hard Blerone XL 2mg and 4mg prolonged release capsules Tolthen XL 2 mg and 4 mg Prolonged-release Capsules, Hard Neditol XL 2 mg and 4 mg, prolonged-release capsules, hard
Name(s) of the active substance(s) (INN)	Tolterodine tartrate
Pharmacotherapeutic classification (ATC code)	Genito urinary system and sex hormones; urinary antispasmodics (G04B D07)
Pharmaceutical form and strength(s)	Prolonged-release capsules, hard, 2 mg and 4 mg.
Reference numbers for the Mutual Recognition Procedure	UK/H/2399-400 and 4752-3/001-2/DC
Reference Member State	United Kingdom
Concerned Member State	UK/H/2399/01/DC (PL 17277/0084): Belgium, Bulgaria, Germany, Denmark, Greece, Spain, Finland, Italy, Iceland, Luxembourg, Malta, Netherlands, Norway and Sweden. UK/H/2399/02/DC (PL 17277/0085): Belgium, Bulgaria, Germany, Denmark, Greece, Spain, Finland, Ireland, Iceland, Luxembourg, Malta, Netherlands, Norway and Sweden UK/H/4752/01-2/DC (PL 17277/0263-44): Czech Republic, Germany, Estonia, Spain, Hungary, Latvia, Lithuania, Romania and Slovakia UK/H/4753/01-2/DC (Pl 17277/0265-6): Belgium, Germany, Italy, Luxembourg, Netherlands and Poland. UK/H/2400/01-2/DC (PL 17277/0271-2): Cyprus, Germany, Greece, Spain, Iceland, Luxembourg and Poland.
Marketing Authorisation Number(s)	PL 17277/0084-5, 263-6 & 271-2.
Name and address of the authorisation holder	Pharmathen S.A., 6 Dervenakion str., Pallini Attki, 153 51 Greece

III SCIENTIFIC OVERVIEW AND DISCUSSION

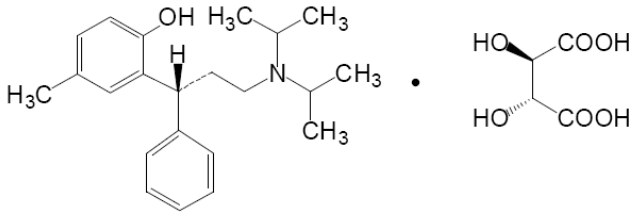
III.1 QUALITY ASPECTS

S. Active substance

INN: Tolterodine tartrate

Chemical names: (4S)-6-chloro-4-(2-cyclopropylethynyl)-4-(trifluoromethyl)-2,4-dihydro-1H-3,1-benzoxazin-2-one
(4S)-6-chloro-4-(cyclopropylethynyl)-1, 4-dihydro -4-trifluoromethyl)-2H-3, 1-benzoxazin-2-one

Structure:



Molecular formula: $C_{26}H_{37}NO_7$

Molecular mass: 475.6

Appearance: Tolterodine tartrate is a white crystalline powder.

Solubility: It is freely soluble in dimethyl formamide, slightly soluble in water, acetone and ethanol and very slightly soluble in ethyl acetate.

Tolterodine tartrate is not the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients lactose monohydrate, cellulose microcrystalline, poly (vinyl acetate), povidone, silica, sodium laurylsulfate, docusate sodium, magnesium stearate (E470b), hydroxypropylmethylcellulose, indigo carmine

(E132), quinoline yellow (E104), titanium dioxide (E171), gelatin, ethylcellulose, triethyl citrate, methacrylic acid - ethyl acrylate copolymer, 1,2-propylene glycol.

All excipients comply with their respective European Pharmacopoeia monographs. In addition the supplier of indigo carmine and quinoline yellow has confirmed that these excipients are in compliance with current European Directives concerning the use of colouring agents in foodstuff. Satisfactory certificates of analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

With the exception of lactose monohydrate, and gelatin none of the excipients contain materials of animal or human origin.

The supplier of lactose monohydrate has confirmed that the lactose is sourced from healthy animals under the same conditions as milk for human consumption.

The suppliers of gelatin have provided Certificates of Suitability from the European Directorate for the Quality of medicines (EDQM) to show that this excipient has been manufactured in-line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE).

No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development
The objective of the development programme was to formulate stable, robust, prolonged-release hard capsules containing 2 mg or 4 mg tolterodine, which could be considered generic/hybrid medicinal products of Detrusitol 2mg and 4mg retard hard capsules (Pharmacia GmbH, Germany).

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial scale and has shown satisfactory results. In addition the Marketing Authorisation Holder (MAH) has committed to perform process validation on future commercial scale batches for all strengths.

Finished Product Specification
The proposed finished product specifications are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided, which comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Container-Closure System
All strengths of the finished product are packaged in:

(1) A cardboard box containing the appropriate number of blisters of transparent polyvinylchloride/polyethylene/polyvinylidene chloride (PVC/PE/PVDC) aluminium foil and an instruction leaflet in pack sizes of:
For PL 17277/0084-85 & 0266:

- Blister packs containing: 7, 14, 28, 30, 49, 50, 56, 80, 84, 90, 98, 100, 112, 160, 280, 320 prolonged-release hard capsules.

For PL 17277/0263:

- Blister packs containing: 14, 28, 84 prolonged-release hard capsules

For PL 17277/0264:

- Blister packs containing: 7, 14, 28, 49, 84, 98 prolonged-release hard capsules

For PL 17277/0265 & 0271:

- Blister packs containing: 14, 28, 56, 84 prolonged-release hard capsules

For PL 17277/0272:

- Blister packs containing: 7, 14, 28, 49, 56, 84, 98,prolonged-release hard capsule

(2) A cardboard box containing a white opaque high density polyethylene (HDPE) bottle containing the appropriate number of capsules with screw cap and an instruction leaflet in pack sizes 30, 100 and 200 capsules (all PL numbers and strengths).

It has been stated that not all pack sizes may be marketed. However, the Marketing Authorisation Holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 24 months for the blister packs and 200 days after first opening the HDPE bottle with the storage condition ‘Do not store above 25°C.’

Bioequivalence/bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPCs, PILs and labels are acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Marketing Authorisation Application (MAA) forms
The MAA forms are satisfactory.

Quality Overall Summary
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
There are no objections to the approval of these products from a pharmaceutical viewpoint.

III.2 NON-CLINICAL ASPECTS

As the pharmacodynamic, pharmacokinetic and toxicological properties of tolterodine are well-known, no new non-clinical studies are required and none have been provided.

The applicant's non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment.

There are no objections to the approval of these products from a non-clinical viewpoint.

III.3 CLINICAL ASPECTS

Pharmacokinetics
In support of these applications, the Marketing Authorisation Holder has submitted the following bioequivalence studies:

STUDY 1
A single centre, randomised, multiple-dose, laboratory-blinded, two-period, two-sequence, crossover study to compare the pharmacokinetics of the test product Tolterodine SR 4mg capsules (Pharmathen S.A) versus the reference product Detrusitol 4mg retard hard capsules (Pharmacia GmbH, Germany) in healthy adult volunteers at steady state.

Volunteers were included in the study in two groups. If the results from the first group were bioequivalent, the study was to be stopped without dosing a second group of subjects. If the results from the first group were not bioequivalent or where drug variability was greater than expected, then the second group was planned for inclusion and dosing. In each study period, all volunteers received a single oral dose of either the test or reference product as a 1 x 4 mg capsule administered after an overnight fast of at least 10 hours for 7 consecutive days. Blood samples were taken for the measurement of pharmacokinetic parameters at pre-dose on day 1 and prior to the 5^{th}, 6^{th} and 7^{th} administration and up to 24 hours post dose of each product. The washout period between treatment periods was at least 7 days.

The pharmacokinetic results for tolterodine (first stage) are presented below (log-transformed values; geometric least square mean and 95% confidence intervals):

Table 7. Comparison of Results with Standards for Bioequivalence – Tolterodine (First Stage)

PARAMETER	INTRA-SUBJECT CV (%)	GEOMETRIC LSMEANS *		RATIO (%)	95% CONFIDENCE LIMITS (%)	
		TEST	REFERENCE		LOWER	UPPER
C_{min}	33.4	484.9	498.1	97.34	79.26	119.54
C_{max}	28.5	2122.4	1845.9	114.98	96.40	137.14
AUC_{τ}	24.0	25137.3	23791.6	105.66	90.97	122.72

* units are pg/mL for C_{min} and C_{max} and pg·h/mL for AUC_{τ}

AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration

The pharmacokinetic results for tolterodine (combined data) are presented below (log-transformed values; geometric least square mean and 95% confidence intervals):

Table 9. Comparison of Results with Standards for Bioequivalence – Tolterodine (Combined Data)

PARAMETER	INTRA-SUBJECT CV (%)	GEOMETRIC LSMEANS *		RATIO (%)	95% CONFIDENCE LIMITS (%)	
		TEST	REFERENCE		LOWER	UPPER
C_{min}	34.2	425.6	398.9	106.70	95.03	119.80
C_{max}	25.5	1801.5	1714.2	105.09	96.44	114.52
AUC_{τ}	20.3	21330.0	20153.3	105.84	98.82	113.36

* units are pg/mL for C_{min} and C_{max} and pg·h/mL for AUC_{τ}

The pharmacokinetic results for the metabolite 5-hydroxymethyl tolterodine (combined data) are presented below (log-transformed values; geometric least square mean and 95% confidence intervals):

Table 11. Comparison of Results with Standards for Bioequivalence – 5-hydroxymethyl tolterodine (Combined Data)

PARAMETER	INTRA-SUBJECT CV (%)	GEOMETRIC LSMEANS *		RATIO (%)	95% CONFIDENCE LIMITS (%)	
		TEST	REFERENCE		LOWER	UPPER
C_{min}	25.7	617.5	591.2	104.45	95.57	114.15
C_{max}	20.3	1933.7	1873.3	103.22	96.36	110.58
AUC_{τ}	14.0	25503.1	24396.6	104.54	99.68	109.63

* units are pg/mL for C_{min} and C_{max} and pg·h/mL for AUC_{τ}

STUDY 2

A single-centre, randomised, single-dose, laboratory-blinded, two-period, two-sequence, crossover study to compare the pharmacokinetics of the test product Tolterodine SR 4mg capsules (Pharmathen S.A) versus the reference product Detrusitol 4mg retard hard capsules (Pharmacia GmbH, Germany) in healthy adult volunteers in the fed state.

Volunteers were included in the study in two groups. If the results from the first group were bioequivalent, the study was to be stopped without dosing a second group of subjects. If the results from the first group were not bioequivalent or where drug variability was greater than expected, then the second group was planned for inclusion and dosing. In each study period, all volunteers received a single oral dose of either the test or reference product as a 1 x 4 mg capsule under fed conditions. Blood samples were taken for the measurement of pharmacokinetic parameters at pre-and up to 60 hours post dose of each product. The washout period between treatment periods was at least 7 days.

The pharmacokinetic results for tolterodine are presented below (log-transformed values; geometric least square mean and 90% and 95% confidence intervals):

Tolterodine

95% Confidence Limits

PARAMETER	INTRA-SUBJECT CV (%)	GEOMETRIC LSMEANS *		RATIO (%)	95% CONFIDENCE LIMITS (%)	
		TEST	REFERENCE		LOWER	UPPER
C_{max}	33.6	1566.2	1584.0	98.88	80.88	120.88
AUC_T	20.2	25502.5	23164.1	110.09	97.37	124.49
AUC_∞	19.0	34414.8	31937.7	107.76	94.30	123.13

* units are pg/mL for C_{max} and pg·h/mL for AUC_T and AUC_∞

90% Confidence Limits

PARAMETER	INTRA-SUBJECT CV (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST	REFERENCE		LOWER	UPPER
C_{max}	33.6	1566.2	1584.0	98.88	83.73	116.76
AUC_T	20.2	25502.5	23164.1	110.09	99.45	121.88
AUC_∞	19.0	34414.8	31937.7	107.76	96.55	120.27

* units are pg/mL for C_{max} and pg·h/mL for AUC_T and AUC_∞

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration

The pharmacokinetic results for metabolite 5-hydroxymethyl tolterodine are presented below (log-transformed values; geometric least square mean and 90% and 95% confidence intervals):

5-hydroxymethyl tolterodine

95% Confidence Limits

PARAMETER	INTRA-SUBJECT CV (%)	GEOMETRIC LSMEANS *		RATIO (%)	95% CONFIDENCE LIMITS (%)	
		TEST	REFERENCE		LOWER	UPPER
C_{max}	22.8	1684.1	1704.7	98.79	85.07	114.73
AUC_T	12.9	30027.1	28699.9	104.62	96.05	113.97
AUC_∞	12.8	31163.2	30017.5	103.82	95.40	112.98

* units are pg/mL for C_{max} and pg·h/mL for AUC_T and AUC_∞

90% Confidence Limits

PARAMETER	INTRA-SUBJECT CV (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST	REFERENCE		LOWER	UPPER
C_{max}	22.8	1684.1	1704.7	98.79	87.32	111.77
AUC_T	12.9	30027.1	28699.9	104.62	97.49	112.28
AUC_∞	12.8	31163.2	30017.5	103.82	96.82	111.32

* units are pg/mL for C_{max} and pg·h/mL for AUC_T and AUC_∞

STUDY 3

A single-centre, randomised, single-dose, laboratory-blinded, two-period, two-sequence, crossover study to compare the pharmacokinetics of the test product Tolterodine SR 4mg capsules (Pharmathen S.A) versus the reference product Detrusitol 4mg retard hard capsules (Pharmacia GmbH, Germany) in healthy adult volunteers in the fasting state.

Volunteers were included in the study in two groups. If the results from the first group were bioequivalent, the study was to be stopped without dosing a second group of subjects. If the results from the first group were not bioequivalent or where drug variability was greater than expected, then the second group was planned for inclusion and dosing. In each study period, all volunteers received a single oral dose of either the test or reference product as a 1 x 4 mg capsule after an overnight fast of at least 10 hours. Blood samples were taken for the measurement of pharmacokinetic parameters at pre-and up to 60 hours post dose of each product. The washout period between treatment periods was at least 7 days.

The pharmacokinetic results for tolterodine are presented below (log-transformed values; geometric least square mean and 90% and 95% confidence intervals):

Table 9. Comparison of Results with Standards for Bioequivalence (95% CI) – Tolterodine

PARAMETER	INTRA-SUBJECT CV (%)	GEOMETRIC LSMEANS *		RATIO (%)	95% CONFIDENCE LIMITS (%)	
		TEST	REFERENCE			TEST
C_{max}	36.0	1402.5	1346.9	104.13	92.93	116.66
AUC_T	29.7	19596.8	18040.9	108.62	98.81	119.41
AUC_∞	29.1	24395.2	22115.0	110.31	100.11	121.55

* units are pg/mL for C_{max} and pg·h/mL for AUC_T and AUC_∞

Table 10. Comparison of Results with 90% CI – Tolterodine

PARAMETER	INTRA-SUBJECT CV (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST	REFERENCE		LOWER	UPPER
C_{max}	36.0	1402.5	1346.9	104.13	94.68	114.51
AUC_T	29.7	19596.8	18040.9	108.62	100.36	117.57
AUC_∞	29.1	24395.2	22115.0	110.31	101.72	119.63

* units are pg/mL for C_{max} and pg·h/mL for AUC_T and AUC_∞

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration

The pharmacokinetic results for metabolite 5-hydroxymethyl tolterodine are presented below (log-transformed values; geometric least square mean and 90% and 95% confidence intervals):

Table 12. Comparison of Results with Standards for Bioequivalence (95% CI) – 5-hydroxymethyl tolterodine

PARAMETER	INTRA-SUBJECT CV (%)	GEOMETRIC LSMEANS *		RATIO (%)	95% CONFIDENCE LIMITS (%)	
		TEST	REFERENCE		LOWER	UPPER
C_{max}	25.1	1666.2	1735.7	95.99	88.24	104.42
AUC_T	20.3	27965.9	26923.8	103.87	97.01	111.22
AUC_∞	19.8	29173.5	28343.0	102.93	96.30	110.02

* units are pg/mL for C_{max} and pg·h/mL for AUC_T and AUC_∞

Table 13. Comparison of Results with 90% CI – 5-hydroxymethyl tolterodine

PARAMETER	INTRA-SUBJECT CV (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST	REFERENCE		LOWER	UPPER
C_{max}	25.1	1666.2	1735.7	95.99	89.47	102.99
AUC_T	20.3	27965.9	26923.8	103.87	98.10	109.98
AUC_∞	19.8	29173.5	28343.0	102.93	97.36	108.82

* units are pg/mL for C_{max} and pg·h/mL for AUC_T and AUC_∞

The assessment of bioequivalence has been based upon 95% confidence intervals for the ratio of the population geometric means (test/reference) for all parameters. As the studies were planned as two-stage studies, this is acceptable.

For the single dose, fed and fasting state studies, the 95% confidence intervals for AUC and C_{max} for test versus reference product for tolterodine and its metabolite, 5-hydroxymethyl tolterodine are within predefined acceptance criteria specified in ”Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev 1/, Corr). Thus, the data support the claim that the test product is bioequivalent to the reference product.
For the multiple dose study, the 95% C_{max}, C_{min} and AUC for test versus reference product for tolterodine and its metabolite 5-hydroxymethyl tolterodine are within predefined acceptance criteria specified in ”Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev 1/, Corr). Thus, the data support the claim that the test product is bioequivalent to the reference product.

As the 2 mg and 4 mg strengths of the product meet the criteria specified in ”Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev 1/, Corr), the results and conclusions of the bioequivalence study on the 4 mg strength can be extrapolated to the 2 mg strength.

Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for these applications.

Efficacy
No new efficacy data were submitted and none were required for these applications.

Safety
With the exception of the data generated during the bioequivalence studies, no new safety data were submitted and none were required for these applications. No new or unexpected safety issues were highlighted by the bioequivalence data.

Summary of Product Characteristics (SmPC), Patient Information Leaflets (PIL) and Labels
The SmPCs, PILs and labels are acceptable. The SmPCs are consistent with that for the originator products. The PIL is consistent with the SmPCs and in line with current guidelines. The labelling is in-line with current guidelines.

MAA Forms
The MAA forms are satisfactory.

Clinical Overview
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a Risk Management Plan for these products.

Conclusion
There are no objections to the approval of these products from a clinical viewpoint.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The quality characteristics of Inconex/Blerone/Tolthen/Neditol 2mg & 4 mg prolonged-release Capsules, Hard are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for applications of this type. The pharmacodynamic, pharmacokinetic and toxicological properties of tolterodine are well-known.

EFFICACY

With the exception of the bioequivalence studies, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant's Tolterodine SR 4mg capsules and its respective reference product Detrusitol 4mg retard hard capsules (Pharmacia GmbH, Germany). As the 2 mg and 4 mg strengths of the product meet the biowaiver criteria specified in "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 Rev 1/, Corr), the results and conclusions of the bioequivalence studies on the 4 mg strength can be extrapolated to the 2 mg strength.

SAFETY

With the exception of the bioequivalence studies, no new data were submitted and none are required for applications of this type. As the safety profile of tolterodine is well-known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence studies.

PRODUCT LITERATURE

The SmPCs, PIL and labelling are satisfactory and consistent with that for the reference products, where appropriate, in line with current guidelines.

BENEFIT-RISK ASSESSMENT

The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence studies support the claim that the applicant's products and the originator products are interchangeable. Extensive clinical experience with tolterodine is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome