Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

TOLTERODINE TARTRATE 1MG AND 2MG FILM-COATED TABLETS

UK/H/1375/001-2/DC
UK/H/1376/001-2/DC
UK Licence No: PL 10880/0119-122

HEXAL AG

LAY SUMMARY

On 20th March 2009, the UK granted Hexal AG Marketing Authorisations (licences) for the prescription only medicinal products Tolterodine Tartrate 1mg and 2mg Film-Coated Tablets (PL 10880/0119-122; UK/H/1375/001-2/DC; UK/H/1376/001-2/DC).

Tolterodine tartrate tablets belong to a group of medicines called urologic muscle relaxants, which relax the bladder muscle.

Tolterodine tartrate is used to treat symptoms of overactive bladder, such as the inability to control urination, the 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 Tolterodine Tartrate 1mg and 2mg Film-Coated Tablets outweigh the risks; hence these Marketing Authorisations have been granted.

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Module 1

Product Name	Tolterodine Tartrate 1mg and 2mg Film-Coated Tablets
Type of Application	Generic, Article 10.1
Active Substance	Tolterodine L-Tartrate
Form	Film-Coated Tablets
Strength	1mg and 2mg
MA Holder	Hexal AG Industriestr. 25, 83607 Holzkirchen, Germany
Reference Member State (RMS)	UK
CMS	Germany, Luxembourg and Spain
Procedure Number	UK/H/1375/001-2/DC; UK/H/1376/001-2/DC
End of Procedure	Day 210 – 04/02/2009

Module 2
Summary of Product Characteristics

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tolterodine Tartrate 1 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains tolterodine tartrate 1 mg corresponding to 0.68 mg tolterodine.
Excipients:
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.
White or almost white, round and biconvex film-coated tablets.
The tablet is engraved with "1" on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

The film-coated tablet should be swallowed whole with a sufficient amount of fluid.
Adults (including elderly):
The recommended dose is 2 mg twice daily. In case of troublesome side effects the dose may be reduced from 2 mg to 1 mg twice daily.

Reduced renal function and hepatic insufficiency:
The recommended dose for patients with impaired liver function or severely impaired renal function (GFR ≤30 ml/min) is 1 mg twice daily (see section 4.4 and 5.2).
The effect of treatment should be re-evaluated after 2–3 months (see section 5.1).

Paediatric patients:
Efficacy of Tolterodine tartrate has not been demonstrated in children (see section 5.1). Therefore, Tolterodine tartrate is not recommended for children.

4.3 Contraindications

Tolterodine tartrate is contraindicated in patients with

- known hypersensitivity to tolterodine tartrate 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 tartrate shall be used with caution in patients with

- significant bladder outlet obstruction at risk of urinary retention
- gastrointestinal obstructive disorders, e.g. pyloric stenosis
- renal impairment (see section 4.2 and 5.2)
- hepatic disease (see section 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 tartrate 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) antiarrhythmics

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

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant systemic medication with potent CYP3A4 inhibitors such as macrolide antibiotics (e.g. erythromycin and clarithromycin), antifungol agents (e.g. ketoconazole and itraconazole) and HIV-protease inhibitors is not recommended due to increase 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 m ore pronounced therapeutic effect and side-effect. Conversely, the therapeutic effect of tolterodine may be reduced by concomitant administration of muscarinic cholinergic receptor agonists.
The effect of prokinetics like metoclopramide and cisapride may be decreased by tolterodine.

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 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 tartrate is not recommended during pregnancy

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Due to the pharmacological effect of tolterodine it may cause mild to moderate antimuscarinic effects, like dryness of the mouth (occurred most commonly in 35 % of patients treated with Tolterodine tartrate and in 10 % of patients treated with placebo), dyspepsia and dry eyes.

The adverse reactions considered at least possibly related to treatment are listed below by body system organ class and absolute frequency. Frequencies are defined as very common (≥1/10); common (>1/100 to <1/10); uncommon (>1/1000 to <1/100); rare (>1/10 000 to <1/1000); very rare (<1/10 000, including isolated cases).

Infections and infestations
Common: Bronchitis.

Immune system disorders
Uncommon: Hypersensitivity not otherwise specified.
Very rare: Anaphylactoid reactions.

Psychiatric disorders
Uncommon: Nervousness.
Rare: Hallucinations,confusion.
Very rare: Disorientation.

Nervous system disorders
Common: Dizziness, somnolence, paresthesia.
Uncommon: Memory impairment.

Eye disorders
Common: Dry eyes, abnormal vision, including abnormal accommodation.

Ear and labyrinth disorders
Common: Vertigo.

Cardiac disorders
Common: Palpitations
Uncommon: Tachycardia, cardiac failure, arrhythmia
Vascular disorders
Very rare: Flushing.

Gastrointestinal disorders
Very common: Dry mouth.
Common: Dyspepsia, constipation, abdominal pain, flatulence, vomiting, diarrhoea.
Uncommon: Gastroesophagal reflux.

Skin and subcutaneous tissue disorders
Common: Dry skin.
Very rare: Angioedema.

Renal and urinary disorders
Common: Dysuria, urinary retention.

General disorders
Very common: Headache.
Common: Fatigue, chest pain, peripheral oedema.

Investigations
Common: Increased weight.

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 patients:
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 single dose. The most severe adverse events observed were accommodation disturbances and micturition difficulties.

In the event of tolterodine overdose, treat with gastric lavage and give activated charcoal.
Treat symptoms as follows:

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urinary antispasmodics
ATC code: G04B D07

Toterodine 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 present compound. In extensive metabolisers this metabolite contributes significantly to the therapeutic effect (see 5.2).
Effect of the treatment can be expected within 4 weeks.

Effect of treatment with tolterodine 2 mg twice daily after 4 and 12 weeks, respectively, compared to placebo (pooled data). Absolute change and percentage change relative to baseline:

Variable	4-week studies			12-week studies		
	Tolterodine 2 mg 2 times daily	Placebo	Statistical significance vs. placebo	Tolterodine 2 mg 2 times daily	Placebo	Statistical significance vs. placebo
Number of micturitions per 24 hours	–1.6 (–14 %) n=392	–0.9 (–8 %) n=189	p≤0.05	–2.3 (–20 %) n=354	–1.4 (–12 %) n=176	p≤0.01
Number of incontinence episodes per 24 hours	–1.3 (–38 %) n=288	–1.0 (–26 %) n=151	not significant	–1.6 (–47 %) n=299	–1.1 (–32 %) n=145	p≤0.05
Mean volume voided per micturition (ml)	+25 (+17 %) n=385	+12 (+8 %) n=185	p≤0.001	+35 (+22 %) n=354	+10 (+6 %) n=176	P≤0.001
Number of patients with no or minimal bladder problems after treatment (%)	16 % n=394	7 % n=190	p≤0.01	19 % n=356	15 % n=177	not significant

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 and 4 mg tolterodine twice daily as the immediate release formulations. The results (Fridericia corrected) at peak tolterodine concentration (1 hour) showed mean QTc interval increases of 5.0 and 11.8 msec for tolterodine doses of 2 mg twice daily and 4 mg twice daily, 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 increase in poor metabolisers (devoid of CYP2D6) treated with tolterodine 2 mg twice daily are comparable to those observed in extensive metabolisers receiving 4 mg twice daily. 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.

Paediatric patients
Efficacy in the paediatric population has not been demonstrated. Two paediatric phase III 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

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

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

Absorption
After oral administration tolterodine is subject to CYP2D6 catalysed first-pass metabolism in the liver, resulting in the formation of the 5-hydroxymethyl derivative, a major pharmacologically equipotent metabolite.

The absolute bioavailability of tolterodine is 17 % in extensive metabolisers, the majority of the patients, and 65 % in poor matabolisers (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 significant higher serum concentrations of tolterodine (about 7-fold) and negligible concentrations of the 5-hydroxymethyl metabolite are observed.

The 5-hydroxymethyl metabolite is pharmacologically active and equipotent with tolterodine. Because of the differences in the protein-binding characteristics of tolterodine and the 5-hydroxymethyl metabolite, the exposure (AUC) of unbound tolterodine in poor metabolisers is similar to the combined

exposure of unbound tolterodine and the 5-hydroxymethyl metabolite in patients with CYP2D6 activity given the same dosage regimen. The safety, tolerability and clinical response are similar irrespective of phenotype.

The excretion of radioactivity after administration of [^{14}C]-tolterodine is about 77 % in urine and 17 % in faeces. Less than 1 % of the dose is recovered as unchanged drug, and about 4 % as the 5-hydroxymethyl metabolite. The carboxylated metabolite and the corresponding dealkylated metabolite account for about 51 % and 29 % of the urinary recovery, respectively.
The pharmacokinetics is linear in the therapeutic dosage range.

Impaired liver function
About 2-fold higher exposure of unbound tolterodine and the 5-hydroxymethyl metabolite is found in subjects with liver cirrhosis (see section 4.2 and 4.4)

Impaired renal function
The mean exposure of unbound tolterodine and its 5-hydroxymethyl metabolite is doubled in patients with severe renal impairment (inulin clearance GFR ≤30 ml/min). The plasma levels of other metabolites were markedly (up to 12-fold) increased in these patients. The clinical relevance of the increased exposure of these metabolites is unknown. There is no data in mild to moderate renal impairment (see section 4.2 and 4.4).

Paediatric patients
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 2-fold higher in children between 5–10 years than in adults (see section 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.
Reproduction studies have been performed in mice and rabbits.

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

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

Tolterodine, as well as its active human metabolites prolong action potential duration (90 % repolarisation) in canine purkinje fibres (14–75 times therapeutic level) 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

Tablet core:
Calcium hydrogen phosphate, anhydrous
Cellulose, microcrystalline
Sodium starch glycolate (Type A)
Silica, colloidal anhydrous
Magnesium stearate

Film coating:
Hypromellose
Titanium dioxide E171
Cellulose, microcrystalline
Stearic acid

6.2 Incompatibilities

Not applicable

6.3 Shelf life
30 months

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
Tablets are packed in either blister package made of Al/PVC and Al/PVC/PVDC or plastic containers and closures made of HDPE.

Pack sizes:
Tolterodine tartrate 1 mg tablets are available in blisters of 7, 14, 28, 30, 50, 56, 60, 84, 98 and 100 film-coated tablets and in bottles of 60 and 500 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Hexal AG,
Industriestrasse 25,
83607 Holzkirchen,
Germany.

8 MARKETING AUTHORISATION NUMBER(S)
PL 10880/0119

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
20/03/2009

10 DATE OF REVISION OF THE TEXT
20/03/2009

1 NAME OF THE MEDICINAL PRODUCT

Tolterodine Tartrate 2 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients:
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.
White or almost white, round and biconvex film-coated tablets.
The tablet is engraved with "2" on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

The film-coated tablet should be swallowed whole with a sufficient amount of fluid.
Adults (including elderly):
The recommended dose is 2 mg twice daily. In case of troublesome side effects the dose may be reduced from 2 mg to 1 mg twice daily.

Reduced renal function and hepatic insufficiency:
The recommended dose for patients with impaired liver function or severely impaired renal function (GFR ≤30 ml/min) is 1 mg twice daily (see section 4.4 and 5.2).
The effect of treatment should be re-evaluated after 2–3 months (see section 5.1).

Paediatric patients:
Efficacy of Tolterodine tartrate has not been demonstrated in children (see section 5.1). Therefore, Tolterodine tartrate is not recommended for children.

4.3 Contraindications

Tolterodine tartrate is contraindicated in patients with

- known hypersensitivity to tolterodine tartrate 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 tartrate shall be used with caution in patients with

- significant bladder outlet obstruction at risk of urinary retention
- gastrointestinal obstructive disorders, e.g. pyloric stenosis
- renal impairment (see section 4.2 and 5.2)
- hepatic disease (see section 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 tartrate 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) antiarrhythmics

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

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant systemic medication with potent CYP3A4 inhibitors such as macrolide antibiotics (e.g. erythromycin and clarithromycin), antifungol agents (e.g. ketoconazole and itraconazole) and HIV-protease inhibitors is not recommended due to increase 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 m ore pronounced therapeutic effect and side-effect. Conversely, the therapeutic effect of tolterodine may be reduced by concomitant administration of muscarinic cholinergic receptor agonists.
The effect of prokinetics like metoclopramide and cisapride may be decreased by tolterodine.

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 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 tartrate is not recommended during pregnancy

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Due to the pharmacological effect of tolterodine it may cause mild to moderate antimuscarinic effects, like dryness of the mouth (occurred most commonly in 35 % of patients treated with Tolterodine tartrate and in 10 % of patients treated with placebo), dyspepsia and dry eyes.

The adverse reactions considered at least possibly related to treatment are listed below by body system organ class and absolute frequency. Frequencies are defined as very common (≥1/10); common (>1/100

to <1/10); uncommon (>1/1000 to <1/100); rare (>1/10 000 to <1/1000); very rare (<1/10 000, including isolated cases).

Infections and infestations
Common: Bronchitis.

Immune system disorders
Uncommon: Hypersensitivity not otherwise specified.
Very rare: Anaphylactoid reactions.

Psychiatric disorders
Uncommon: Nervousness.
Rare: Hallucinations,confusion.
Very rare: Disorientation.

Nervous system disorders
Common: Dizziness, somnolence, paresthesia.
Uncommon: Memory impairment.

Eye disorders
Common: Dry eyes, abnormal vision, including abnormal accommodation.

Ear and labyrinth disorders
Common: Vertigo.

Cardiac disorders
Common: Palpitations
Uncommon: Tachycardia, cardiac failure, arrhythmia
Vascular disorders
Very rare: Flushing.

Gastrointestinal disorders
Very common: Dry mouth.
Common: Dyspepsia, constipation, abdominal pain, flatulence, vomiting, diarrhoea.
Uncommon: Gastroesophagal reflux.

Skin and subcutaneous tissue disorders
Common: Dry skin.
Very rare: Angioedema.

Renal and urinary disorders
Common: Dysuria, urinary retention.

General disorders
Very common: Headache.
Common: Fatigue, chest pain, peripheral oedema.

Investigations
Common: Increased weight.

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 patients:
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 single dose. The most severe adverse events observed were accommodation disturbances and micturition difficulties.

In the event of tolterodine overdose, treat with gastric lavage and give activated charcoal.
Treat symptoms as follows:

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urinary antispasmodics
ATC code: G04B D07

Toterodine 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 present compound. In extensive metabolisers this metabolite contributes significantly to the therapeutic effect (see 5.2).
Effect of the treatment can be expected within 4 weeks.

Effect of treatment with tolterodine 2 mg twice daily after 4 and 12 weeks, respectively, compared to placebo (pooled data). Absolute change and percentage change relative to baseline:

Variable	4-week studies			12-week studies		
	Tolterodine 2 mg 2 times daily	Placebo	Statistical significance vs. placebo	Tolterodine 2 mg 2 times daily	Placebo	Statistical significance vs. placebo
Number of micturitions per 24 hours	–1.6 (–14 %) n=392	–0.9 (–8 %) n=189	p≤0.05	–2.3 (–20 %) n=354	–1.4 (–12 %) n=176	p≤0.01
Number of incontinence episodes per 24 hours	–1.3 (–38 %) n=288	–1.0 (–26 %) n=151	not significant	–1.6 (–47 %) n=299	–1.1 (–32 %) n=145	p≤0.05
Mean volume voided per micturition (ml)	+25 (+17 %) n=385	+12 (+8 %) n=185	p≤0.001	+35 (+22 %) n=354	+10 (+6 %) n=176	P≤0.001
Number of patients with no or minimal bladder problems after treatment (%)	16 % n=394	7 % n=190	p≤0.01	19 % n=356	15 % n=177	not significant

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 and 4 mg tolterodine twice daily as the immediate release formulations. The results (Fridericia corrected) at peak tolterodine concentration (1 hour) showed mean QTc interval increases of 5.0 and 11.8 msec for tolterodine doses of 2 mg twice daily and 4 mg twice daily, 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 increase in poor metabolisers (devoid of CYP2D6) treated with tolterodine 2 mg twice daily are comparable to those observed in extensive metabolisers receiving 4 mg twice daily. 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.

Paediatric patients
Efficacy in the paediatric population has not been demonstrated. Two paediatric phase III 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

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

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

Absorption
After oral administration tolterodine is subject to CYP2D6 catalysed first-pass metabolism in the liver, resulting in the formation of the 5-hydroxymethyl derivative, a major pharmacologically equipotent metabolite.

The absolute bioavailability of tolterodine is 17 % in extensive metabolisers, the majority of the patients, and 65 % in poor matabolisers (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 significant higher serum concentrations of tolterodine (about 7-fold) and negligible concentrations of the 5-hydroxymethyl metabolite are observed.

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

The excretion of radioactivity after administration of [^{14}C]-tolterodine is about 77 % in urine and 17 % in faeces. Less than 1 % of the dose is recovered as unchanged drug, and about 4 % as the 5-hydroxymethyl metabolite. The carboxylated metabolite and the corresponding dealkylated metabolite account for about 51 % and 29 % of the urinary recovery, respectively.
The pharmacokinetics is linear in the therapeutic dosage range.

Impaired liver function
About 2-fold higher exposure of unbound tolterodine and the 5-hydroxymethyl metabolite is found in subjects with liver cirrhosis (see section 4.2 and 4.4)

Impaired renal function
The mean exposure of unbound tolterodine and its 5-hydroxymethyl metabolite is doubled in patients with severe renal impairment (inulin clearance GFR ≤30 ml/min). The plasma levels of other metabolites were markedly (up to 12-fold) increased in these patients. The clinical relevance of the increased exposure of these metabolites is unknown. There is no data in mild to moderate renal impairment (see section 4.2 and 4.4).

Paediatric patients
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 2-fold higher in children between 5–10 years than in adults (see section 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.
Reproduction studies have been performed in mice and rabbits.

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

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

Tolterodine, as well as its active human metabolites prolong action potential duration (90 % repolarisation) in canine purkinje fibres (14–75 times therapeutic level) 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

Tablet core:
Calcium hydrogen phosphate, anhydrous
Cellulose, microcrystalline
Sodium starch glycolate (Type A)
Silica, colloidal anhydrous
Magnesium stearate

Film coating:
Hypromellose
Titanium dioxide E171
Cellulose, microcrystalline
Stearic acid

6.2 Incompatibilities

Not applicable

6.3 Shelf life

30 months

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
Tablets are packed in either blister package made of Al/PVC and Al/PVC/PVDC or plastic containers and closures made of HDPE.

Pack sizes:
Tolterodine tartrate 2 mg tablets are available in blisters of 7, 14, 28, 30, 50, 56, 60, 84, 98 and 100 film-coated tablets and in bottles of 60 and 500 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Hexal AG,
Industriestrasse 25,
83607 Holzkirchen,
Germany.

8 MARKETING AUTHORISATION NUMBER(S)
PL 10880/0120

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
20/03/2009

10 DATE OF REVISION OF THE TEXT
20/03/2009

1 NAME OF THE MEDICINAL PRODUCT

Tolterodine Tartrate 1 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains tolterodine tartrate 1 mg corresponding to 0.68 mg tolterodine.
Excipients:
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.
White or almost white, round and biconvex film-coated tablets.
The tablet is engraved with "1" on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

The film-coated tablet should be swallowed whole with a sufficient amount of fluid.
Adults (including elderly):
The recommended dose is 2 mg twice daily. In case of troublesome side effects the dose may be reduced from 2 mg to 1 mg twice daily.

Reduced renal function and hepatic insufficiency:
The recommended dose for patients with impaired liver function or severely impaired renal function (GFR ≤30 ml/min) is 1 mg twice daily (see section 4.4 and 5.2).
The effect of treatment should be re-evaluated after 2–3 months (see section 5.1).

Paediatric patients:
Efficacy of Tolterodine tartrate has not been demonstrated in children (see section 5.1). Therefore, Tolterodine tartrate is not recommended for children.

4.3 Contraindications

Tolterodine tartrate is contraindicated in patients with

- known hypersensitivity to tolterodine tartrate 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 tartrate shall be used with caution in patients with

- significant bladder outlet obstruction at risk of urinary retention
- gastrointestinal obstructive disorders, e.g. pyloric stenosis
- renal impairment (see section 4.2 and 5.2)
- hepatic disease (see section 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 tartrate 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) antiarrhythmics

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

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant systemic medication with potent CYP3A4 inhibitors such as macrolide antibiotics (e.g. erythromycin and clarithromycin), antifungol agents (e.g. ketoconazole and itraconazole) and HIV-protease inhibitors is not recommended due to increase 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 m ore pronounced therapeutic effect and side-effect. Conversely, the therapeutic effect of tolterodine may be reduced by concomitant administration of muscarinic cholinergic receptor agonists.
The effect of prokinetics like metoclopramide and cisapride may be decreased by tolterodine.

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 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 tartrate is not recommended during pregnancy

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Due to the pharmacological effect of tolterodine it may cause mild to moderate antimuscarinic effects, like dryness of the mouth (occurred most commonly in 35 % of patients treated with Tolterodine tartrate and in 10 % of patients treated with placebo), dyspepsia and dry eyes.

The adverse reactions considered at least possibly related to treatment are listed below by body system organ class and absolute frequency. Frequencies are defined as very common (≥1/10); common (>1/100

to <1/10); uncommon (>1/1000 to <1/100); rare (>1/10 000 to <1/1000); very rare (<1/10 000, including isolated cases).

Infections and infestations
Common: Bronchitis.

Immune system disorders
Uncommon: Hypersensitivity not otherwise specified.
Very rare: Anaphylactoid reactions.

Psychiatric disorders
Uncommon: Nervousness.
Rare: Hallucinations,confusion.
Very rare: Disorientation.

Nervous system disorders
Common: Dizziness, somnolence, paresthesia.
Uncommon: Memory impairment.

Eye disorders
Common: Dry eyes, abnormal vision, including abnormal accommodation.

Ear and labyrinth disorders
Common: Vertigo.

Cardiac disorders
Common: Palpitations
Uncommon: Tachycardia, cardiac failure, arrhythmia
Vascular disorders
Very rare: Flushing.

Gastrointestinal disorders
Very common: Dry mouth.
Common: Dyspepsia, constipation, abdominal pain, flatulence, vomiting, diarrhoea.
Uncommon: Gastroesophagal reflux.

Skin and subcutaneous tissue disorders
Common: Dry skin.
Very rare: Angioedema.

Renal and urinary disorders
Common: Dysuria, urinary retention.

General disorders
Very common: Headache.
Common: Fatigue, chest pain, peripheral oedema.

Investigations
Common: Increased weight.

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 patients:
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 single dose. The most severe adverse events observed were accommodation disturbances and micturition difficulties.

In the event of tolterodine overdose, treat with gastric lavage and give activated charcoal.
Treat symptoms as follows:

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urinary antispasmodics
ATC code: G04B D07

Toterodine 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 present compound. In extensive metabolisers this metabolite contributes significantly to the therapeutic effect (see 5.2).
Effect of the treatment can be expected within 4 weeks.

Effect of treatment with tolterodine 2 mg twice daily after 4 and 12 weeks, respectively, compared to placebo (pooled data). Absolute change and percentage change relative to baseline:

Variable	4-week studies			12-week studies		
	Tolterodine 2 mg 2 times daily	Placebo	Statistical significance vs. placebo	Tolterodine 2 mg 2 times daily	Placebo	Statistical significance vs. placebo
Number of micturitions per 24 hours	–1.6 (–14 %) n=392	–0.9 (–8 %) n=189	p≤0.05	–2.3 (–20 %) n=354	–1.4 (–12 %) n=176	p≤0.01
Number of incontinence episodes per 24 hours	–1.3 (–38 %) n=288	–1.0 (–26 %) n=151	not significant	–1.6 (–47 %) n=299	–1.1 (–32 %) n=145	p≤0.05
Mean volume voided per micturition (ml)	+25 (+17 %) n=385	+12 (+8 %) n=185	p≤0.001	+35 (+22 %) n=354	+10 (+6 %) n=176	P≤0.001
Number of patients with no or minimal bladder problems after treatment (%)	16 % n=394	7 % n=190	p≤0.01	19 % n=356	15 % n=177	not significant

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 and 4 mg tolterodine twice daily as the immediate release formulations. The results (Fridericia corrected) at peak tolterodine concentration (1 hour) showed mean QTc interval increases of 5.0 and 11.8 msec for tolterodine doses of 2 mg twice daily and 4 mg twice daily, 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 increase in poor metabolisers (devoid of CYP2D6) treated with tolterodine 2 mg twice daily are comparable to those observed in extensive metabolisers receiving 4 mg twice daily. 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.

Paediatric patients
Efficacy in the paediatric population has not been demonstrated. Two paediatric phase III 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

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

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

Absorption
After oral administration tolterodine is subject to CYP2D6 catalysed first-pass metabolism in the liver, resulting in the formation of the 5-hydroxymethyl derivative, a major pharmacologically equipotent metabolite.

The absolute bioavailability of tolterodine is 17 % in extensive metabolisers, the majority of the patients, and 65 % in poor matabolisers (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 significant higher serum concentrations of tolterodine (about 7-fold) and negligible concentrations of the 5-hydroxymethyl metabolite are observed.

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

The excretion of radioactivity after administration of [^{14}C]-tolterodine is about 77 % in urine and 17 % in faeces. Less than 1 % of the dose is recovered as unchanged drug, and about 4 % as the 5-hydroxymethyl metabolite. The carboxylated metabolite and the corresponding dealkylated metabolite account for about 51 % and 29 % of the urinary recovery, respectively.
The pharmacokinetics is linear in the therapeutic dosage range.

Impaired liver function
About 2-fold higher exposure of unbound tolterodine and the 5-hydroxymethyl metabolite is found in subjects with liver cirrhosis (see section 4.2 and 4.4)

Impaired renal function
The mean exposure of unbound tolterodine and its 5-hydroxymethyl metabolite is doubled in patients with severe renal impairment (inulin clearance GFR ≤30 ml/min). The plasma levels of other metabolites were markedly (up to 12-fold) increased in these patients. The clinical relevance of the increased exposure of these metabolites is unknown. There is no data in mild to moderate renal impairment (see section 4.2 and 4.4).

Paediatric patients
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 2-fold higher in children between 5–10 years than in adults (see section 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.
Reproduction studies have been performed in mice and rabbits.

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

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

Tolterodine, as well as its active human metabolites prolong action potential duration (90 % repolarisation) in canine purkinje fibres (14–75 times therapeutic level) 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

Tablet core:
Calcium hydrogen phosphate, anhydrous
Cellulose, microcrystalline
Sodium starch glycolate (Type A)
Silica, colloidal anhydrous
Magnesium stearate

Film coating:
Hypromellose
Titanium dioxide E171
Cellulose, microcrystalline
Stearic acid

6.2 Incompatibilities

Not applicable

6.3 Shelf life

30 months

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
Tablets are packed in either blister package made of Al/PVC and Al/PVC/PVDC or plastic containers and closures made of HDPE.

Pack sizes:
Tolterodine tartrate 1 mg tablets are available in blisters of 7, 14, 28, 30, 50, 56, 60, 84, 98 and 100 film-coated tablets and in bottles of 60 and 500 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Hexal AG,
Industriestrasse 25,
83607 Holzkirchen,
Germany.

8 MARKETING AUTHORISATION NUMBER(S)
PL 10880/0121

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
20/03/2009

10 DATE OF REVISION OF THE TEXT
20/03/2009

1 NAME OF THE MEDICINAL PRODUCT

Tolterodine Tartrate 2 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains tolterodine tartrate 2 mg corresponding to 1.37 mg tolterodine, respectively.
Excipients:
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.
White or almost white, round and biconvex film-coated tablets.
The tablet is engraved with "2" on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

The film-coated tablet should be swallowed whole with a sufficient amount of fluid.
Adults (including elderly):
The recommended dose is 2 mg twice daily. In case of troublesome side effects the dose may be reduced from 2 mg to 1 mg twice daily.

Reduced renal function and hepatic insufficiency:
The recommended dose for patients with impaired liver function or severely impaired renal function (GFR ≤30 ml/min) is 1 mg twice daily (see section 4.4 and 5.2).
The effect of treatment should be re-evaluated after 2–3 months (see section 5.1).

Paediatric patients:
Efficacy of Tolterodine tartrate has not been demonstrated in children (see section 5.1). Therefore, Tolterodine tartrate is not recommended for children.

4.3 Contraindications

Tolterodine tartrate is contraindicated in patients with

- known hypersensitivity to tolterodine tartrate 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 tartrate shall be used with caution in patients with

- significant bladder outlet obstruction at risk of urinary retention
- gastrointestinal obstructive disorders, e.g. pyloric stenosis
- renal impairment (see section 4.2 and 5.2)
- hepatic disease (see section 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 tartrate 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) antiarrhythmics

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

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant systemic medication with potent CYP3A4 inhibitors such as macrolide antibiotics (e.g. erythromycin and clarithromycin), antifungol agents (e.g. ketoconazole and itraconazole) and HIV-protease inhibitors is not recommended due to increase 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 m ore pronounced therapeutic effect and side-effect. Conversely, the therapeutic effect of tolterodine may be reduced by concomitant administration of muscarinic cholinergic receptor agonists.
The effect of prokinetics like metoclopramide and cisapride may be decreased by tolterodine.

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 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 tartrate is not recommended during pregnancy

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Due to the pharmacological effect of tolterodine it may cause mild to moderate antimuscarinic effects, like dryness of the mouth (occurred most commonly in 35 % of patients treated with Tolterodine tartrate and in 10 % of patients treated with placebo), dyspepsia and dry eyes.

The adverse reactions considered at least possibly related to treatment are listed below by body system organ class and absolute frequency. Frequencies are defined as very common (≥1/10); common (>1/100

to <1/10); uncommon (>1/1000 to <1/100); rare (>1/10 000 to <1/1000); very rare (<1/10 000, including isolated cases).

Infections and infestations
Common: Bronchitis.

Immune system disorders
Uncommon: Hypersensitivity not otherwise specified.
Very rare: Anaphylactoid reactions.

Psychiatric disorders
Uncommon: Nervousness.
Rare: Hallucinations,confusion.
Very rare: Disorientation.

Nervous system disorders
Common: Dizziness, somnolence, paresthesia.
Uncommon: Memory impairment.

Eye disorders
Common: Dry eyes, abnormal vision, including abnormal accommodation.

Ear and labyrinth disorders
Common: Vertigo.

Cardiac disorders
Common: Palpitations
Uncommon: Tachycardia, cardiac failure, arrhythmia
Vascular disorders
Very rare: Flushing.

Gastrointestinal disorders
Very common: Dry mouth.
Common: Dyspepsia, constipation, abdominal pain, flatulence, vomiting, diarrhoea.
Uncommon: Gastroesophagal reflux.

Skin and subcutaneous tissue disorders
Common: Dry skin.
Very rare: Angioedema.

Renal and urinary disorders
Common: Dysuria, urinary retention.

General disorders
Very common: Headache.
Common: Fatigue, chest pain, peripheral oedema.

Investigations
Common: Increased weight.

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 patients:
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 single dose. The most severe adverse events observed were accommodation disturbances and micturition difficulties.

In the event of tolterodine overdose, treat with gastric lavage and give activated charcoal.
Treat symptoms as follows:

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urinary antispasmodics
ATC code: G04B D07

Toterodine 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 present compound. In extensive metabolisers this metabolite contributes significantly to the therapeutic effect (see 5.2).
Effect of the treatment can be expected within 4 weeks.

Effect of treatment with tolterodine 2 mg twice daily after 4 and 12 weeks, respectively, compared to placebo (pooled data). Absolute change and percentage change relative to baseline:

Variable	4-week studies			12-week studies		
	Tolterodine 2 mg 2 times daily	Placebo	Statistical significance vs. placebo	Tolterodine 2 mg 2 times daily	Placebo	Statistical significance vs. placebo
Number of micturitions per 24 hours	–1.6 (–14 %) n=392	–0.9 (–8 %) n=189	p≤0.05	–2.3 (–20 %) n=354	–1.4 (–12 %) n=176	p≤0.01
Number of incontinence episodes per 24 hours	–1.3 (–38 %) n=288	–1.0 (–26 %) n=151	not significant	–1.6 (–47 %) n=299	–1.1 (–32 %) n=145	p≤0.05
Mean volume voided per micturition (ml)	+25 (+17 %) n=385	+12 (+8 %) n=185	p≤0.001	+35 (+22 %) n=354	+10 (+6 %) n=176	P≤0.001
Number of patients with no or minimal bladder problems after treatment (%)	16 % n=394	7 % n=190	p≤0.01	19 % n=356	15 % n=177	not significant

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 and 4 mg tolterodine twice daily as the immediate release formulations. The results (Fridericia corrected) at peak tolterodine concentration (1 hour) showed mean QTc interval increases of 5.0 and 11.8 msec for tolterodine doses of 2 mg twice daily and 4 mg twice daily, 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 increase in poor metabolisers (devoid of CYP2D6) treated with tolterodine 2 mg twice daily are comparable to those observed in extensive metabolisers receiving 4 mg twice daily. 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.

Paediatric patients
Efficacy in the paediatric population has not been demonstrated. Two paediatric phase III 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

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

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

Absorption
After oral administration tolterodine is subject to CYP2D6 catalysed first-pass metabolism in the liver, resulting in the formation of the 5-hydroxymethyl derivative, a major pharmacologically equipotent metabolite.

The absolute bioavailability of tolterodine is 17 % in extensive metabolisers, the majority of the patients, and 65 % in poor matabolisers (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 significant higher serum concentrations of tolterodine (about 7-fold) and negligible concentrations of the 5-hydroxymethyl metabolite are observed.

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

The excretion of radioactivity after administration of [^{14}C]-tolterodine is about 77 % in urine and 17 % in faeces. Less than 1 % of the dose is recovered as unchanged drug, and about 4 % as the 5-hydroxymethyl metabolite. The carboxylated metabolite and the corresponding dealkylated metabolite account for about 51 % and 29 % of the urinary recovery, respectively.
The pharmacokinetics is linear in the therapeutic dosage range.

Impaired liver function
About 2-fold higher exposure of unbound tolterodine and the 5-hydroxymethyl metabolite is found in subjects with liver cirrhosis (see section 4.2 and 4.4)

Impaired renal function
The mean exposure of unbound tolterodine and its 5-hydroxymethyl metabolite is doubled in patients with severe renal impairment (inulin clearance GFR ≤30 ml/min). The plasma levels of other metabolites were markedly (up to 12-fold) increased in these patients. The clinical relevance of the increased exposure of these metabolites is unknown. There is no data in mild to moderate renal impairment (see section 4.2 and 4.4).

Paediatric patients
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 2-fold higher in children between 5–10 years than in adults (see section 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.
Reproduction studies have been performed in mice and rabbits.

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

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

Tolterodine, as well as its active human metabolites prolong action potential duration (90 % repolarisation) in canine purkinje fibres (14–75 times therapeutic level) 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

Tablet core:
Calcium hydrogen phosphate, anhydrous
Cellulose, microcrystalline
Sodium starch glycolate (Type A)
Silica, colloidal anhydrous
Magnesium stearate

Film coating:
Hypromellose
Titanium dioxide E171
Cellulose, microcrystalline
Stearic acid

6.2 Incompatibilities

Not applicable

6.3 Shelf life

30 months

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
Tablets are packed in either blister package made of Al/PVC and Al/PVC/PVDC or plastic containers and closures made of HDPE.

Pack sizes:
Tolterodine tartrate 2 mg tablets are available in blisters of 7, 14, 28, 30, 50, 56, 60, 84, 98 and 100 film-coated tablets and in bottles of 60 and 500 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Hexal AG,
Industriestrasse 25,
83607 Holzkirchen,
Germany.

8 MARKETING AUTHORISATION NUMBER(S)
PL 10880/0122

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
20/03/2009

10 DATE OF REVISION OF THE TEXT
20/03/2009

Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER item code

Tolterodine Tartrate 1 mg film-coated Tablets
Tolterodine Tartrate 2 mg film-coated Tablets

Tolterodine tartrate

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your 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 gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

SANDOZ

1 What Tolterodine tartrate is and what it is used for

Tolterodine tartrate is used to **treat symptoms of overactive bladder**, such as:
- inability to control urination
- need to rush to the toilet with no advance warning and/or go to the toilet frequently

Tolterodine tartrate belongs to a class of urologic muscle relaxants, which relax the bladder muscle.

2 Before you take Tolterodine tartrate

Do not take Tolterodine tartrate
if you are/have:
- **allergic** (hypersensitive) **to tolterodine tartrate** or any of the other ingredients
- **inability to empty the bladder**
- a chronic **ulcerative and inflammatory bowel** disease (severe ulcerative colitis)
- **increased eye pressure** with loss of eyesight that is not being adequately treated (uncontrolled narrow-angle glaucoma)
- a certain **muscle weakness**, called Myasthenia gravis
- an acute **enlargement of the colon** (toxic megacolon)

Take special care with Tolterodine tartrate
if you have:
- difficulty passing urine and poor urine output
- a very swollen, painful stomach, affecting swallowing and digesting
- kidney or liver problems
  See chapter 3 "How to take Tolterodine tartrate".
- a nerve problem which sometimes occurs with diabetes and can lead to diarrhoea, impotence or low blood pressure (Autonomic neuropathy)
- hiatus hernia, where part of your stomach protrudes through the diaphragm
- have or previously have had severe constipation.
- a certain heart beat abnormality known as QT prolongation
- abnormally low levels of potassium, magnesium or calcium in your blood
- a pulse rate of less than 60 beats per minute
- heart diseases, such as heart muscle disturbance, reduced blood flow to the heart muscle, irregular heartbeat or heart failure

Please **tell your doctor or pharmacist** before taking this medicine if any of the above apply to you.

Children, under 18 years
Tolterodine tartrate is not recommended for children.

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

The following medicines can influence, or be influenced by, Tolterodine tartrate:
- **medicines to treat irregular heart beat,** such as quinidine, procainamide, amiodarone, sotalol
- macrolide antibiotics, such as **erythromycin, clarithromycin**
- medicines to treat fungal infections, such as **ketoconazole, itraconazole**
- **medicines to treat HIV** containing active substances with names ending in "-navir"
- **metoclopramide, cisapride** (medicines to increase intestinal motility)

Medicines with a similar mode of action (antimuscarinic properties) or medicines with an opposite mode of action (cholinergic properties) to Tolterodine tartrate could possibly interact with Tolterodine tartrate. Examples are:
- medicines which dilate the eye pupil, such as atropine, scopolamine, tropicamid
- medicines to lower pressure in the eye, such as carbachol, pilocarpine
- medicines to treat Parkinson disease, such as biperiden, bornaprin, metixen, procyclidin, trihexyphenidyl
- medicines to treat spasms of the stomach, bowel, bladder, genitals or the bronchial tubes, such as butylscopolaminium, ipratropium, tiotropium
- medicines to treat bladder and bowel muscle disturbances, such as oxybutynin, trospium, solifenacin, darifenacin, bethanechol.

Pregnancy and breast-feeding
There is insufficient experience with the use of Tolterodine tartrate during pregnancy. As Tolterodine tartrate may harm your unborn child, **you should not use** Tolterodine tartrate when you are pregnant. Tell your doctor immediately if you are pregnant, think you are pregnant or are planning to become pregnant.

It is not known if the active substance in Tolterodine tartrate is excreted into mother's milk. Therefore, **you should not take** Tolterodine tartrate if you are breast-feeding.

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

Driving and using machines
Tolterodine tartrate may cause dizziness, fatigue and blurred vision. **Do not drive or operate machinery** if this affects you.

3 How to take Tolterodine tartrate

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

The **usual dose** is: **2 mg twice daily** (given as two 1 mg tablets or one 2 mg tablet twice daily).

In the case of impaired kidney or liver function or troublesome side effects the usual dose is 1 mg twice daily.

Continued over the page>>

Administration
Take the tablets whole with one glass of water independent of meals in the morning and in the evening.

Duration of use
To be **decided by** your attending **doctor**.

Do not stop treatment early because you do not see an immediate effect. Your bladder will need some time to adapt. Your doctor will evaluate the effect of your treatment after 2-3 months.

If you take more Tolterodine tartrate than you should
If you have taken too much Tolterodine tartrate, contact your doctor or pharmacist immediately.

If you forget to take Tolterodine tartrate
If you forget to take a dose, take the next dose normally, when it is due. Do not take a double dose to compensate the forgotten dose.

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 tartrate 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 throat
- difficulty to swallow
- hives and difficulty in breathing

Side effects can occur with the following frequencies:

Very common, occurs in more than 1 per 10 users:
- dry mouth
  This may occur in 35% of patients.
- headache

Common, occurs in 1 to 10 per 100 users:
- constipation
- abdominal pain
- dizziness
- sleepiness
- decreased tear production, causing dry irritable eyes
- fatigue
- drowsiness
- altered sensation - pins and needles
- blurred vision
- vertigo
- chest pain
- flatulence
- vomiting
- diarrhoea
- pain or difficulty in passing urine
- inability to empty the bladder
- dry skin
- palpitations
- bronchitis
- extra fluid in the body causing swollen hands, ankles and/or feet
- increased weight

Uncommon, occurs in 1 to 10 per 1,000 users:
- allergic reactions
- heartburn
- nervousness
- memory impairment
- increased heart activity
- irregular heartbeat
- heart failure

Rare, occurs in 1 to 10 per 10,000 users:
- hallucinations
- confusion

Very rare, occurs in fewer than 1 per 10,000 users:
- severe allergic reactions including swelling mainly of the face and throat
- flushed skin
- disorientation

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 tartrate

Keep out of the reach and sight of children.

This medicinal product does not require any special storage conditions.

Do not use Tolterodine tartrate after the expiry date which is stated on the blister and carton after "EXP". The expiry date refers to the last day of that month.

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 tartrate contains
- The **active substance** is **tolterodine tartrate**.
  One tablet contains 1 mg of tolterodine tartrate, equivalent to 0.68 mg of tolterodine.
  One tablet contains 2 mg of tolterodine tartrate, equivalent to 1.37 mg of tolterodine.
- The other ingredients are:
  Tablet core: cellulose, microcrystalline; calcium hydrogen phosphate, anhydrous; sodium starch glycolate (Type A); magnesium stearate; silica, colloidal anhydrous.
  Tablet coating: cellulose, microcrystalline; hypromellose; stearic acid; titanium dioxide (E171).

What Tolterodine tartrate looks like and contents of the pack
Tolterodine tartrate 1 mg tablets are white or almost white, round and biconvex film-coated tablets, coded with "1" on one side.
Tolterodine tartrate 2 mg tablets are white or almost white, round and biconvex film-coated tablets, coded with "2" on one side.

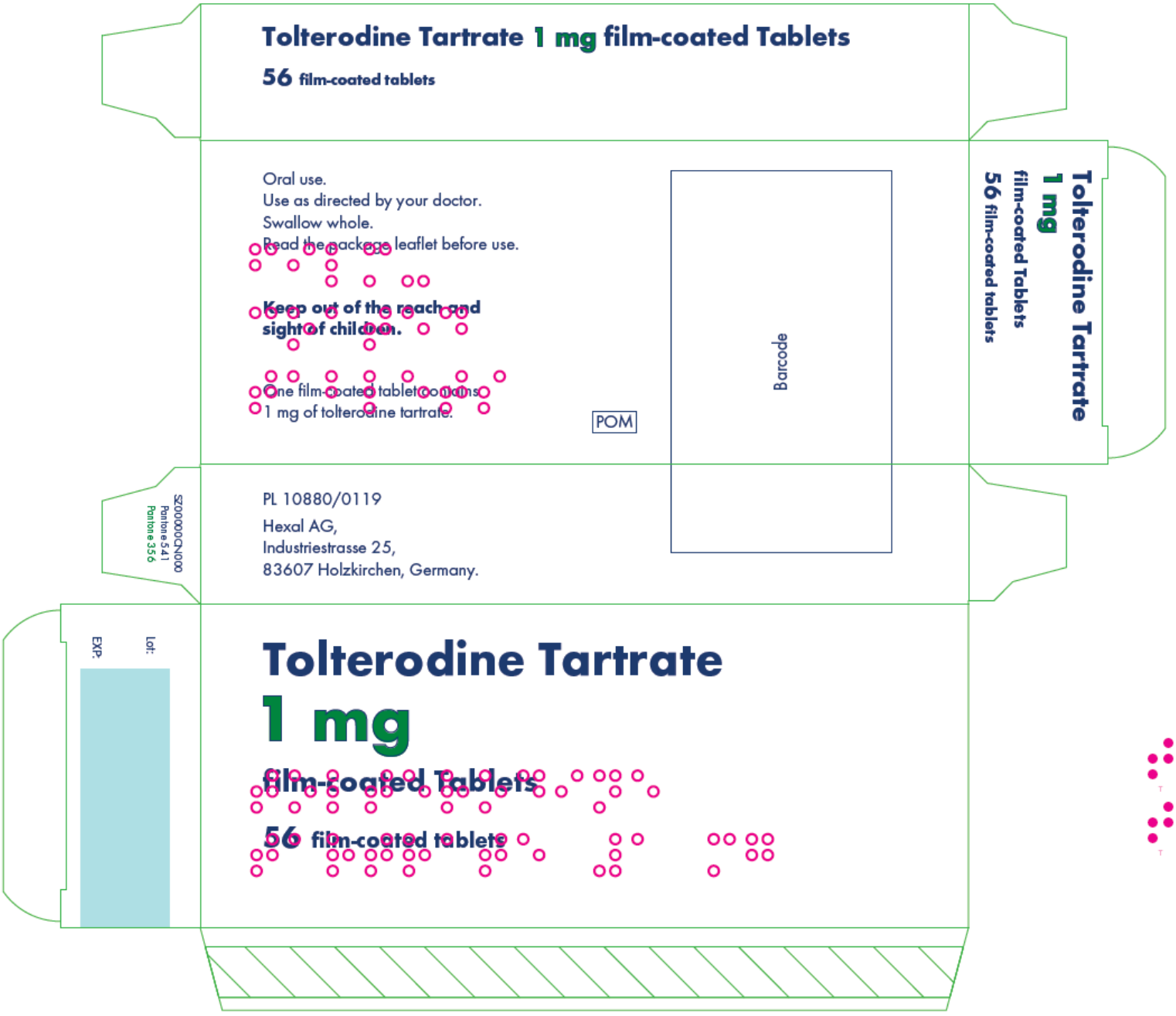
The film-coated tablets are supplied in blister packs or plastic bottles containing 7, 14, 28, 30, 50, 56, 60, 84, 98, 100 and 500 film-coated tablets.

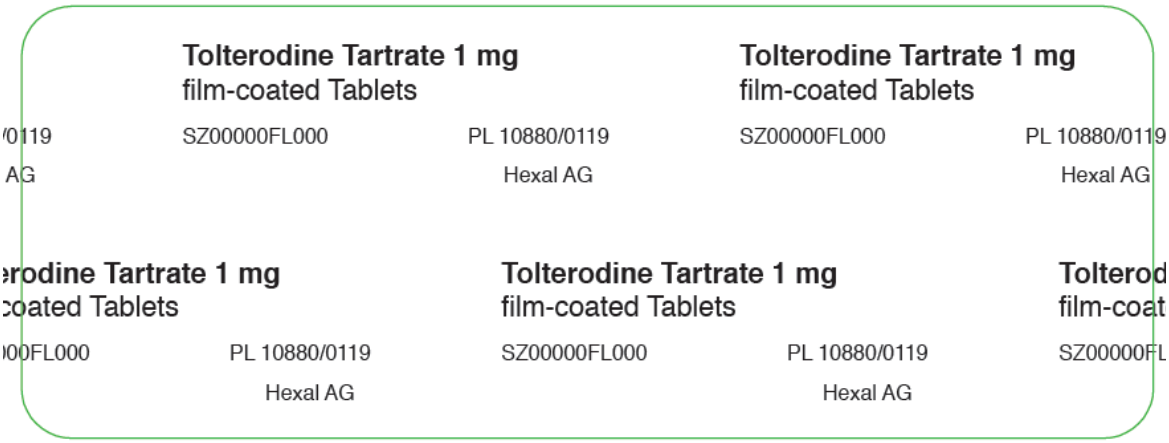
Not all pack sizes or containers may be marketed.

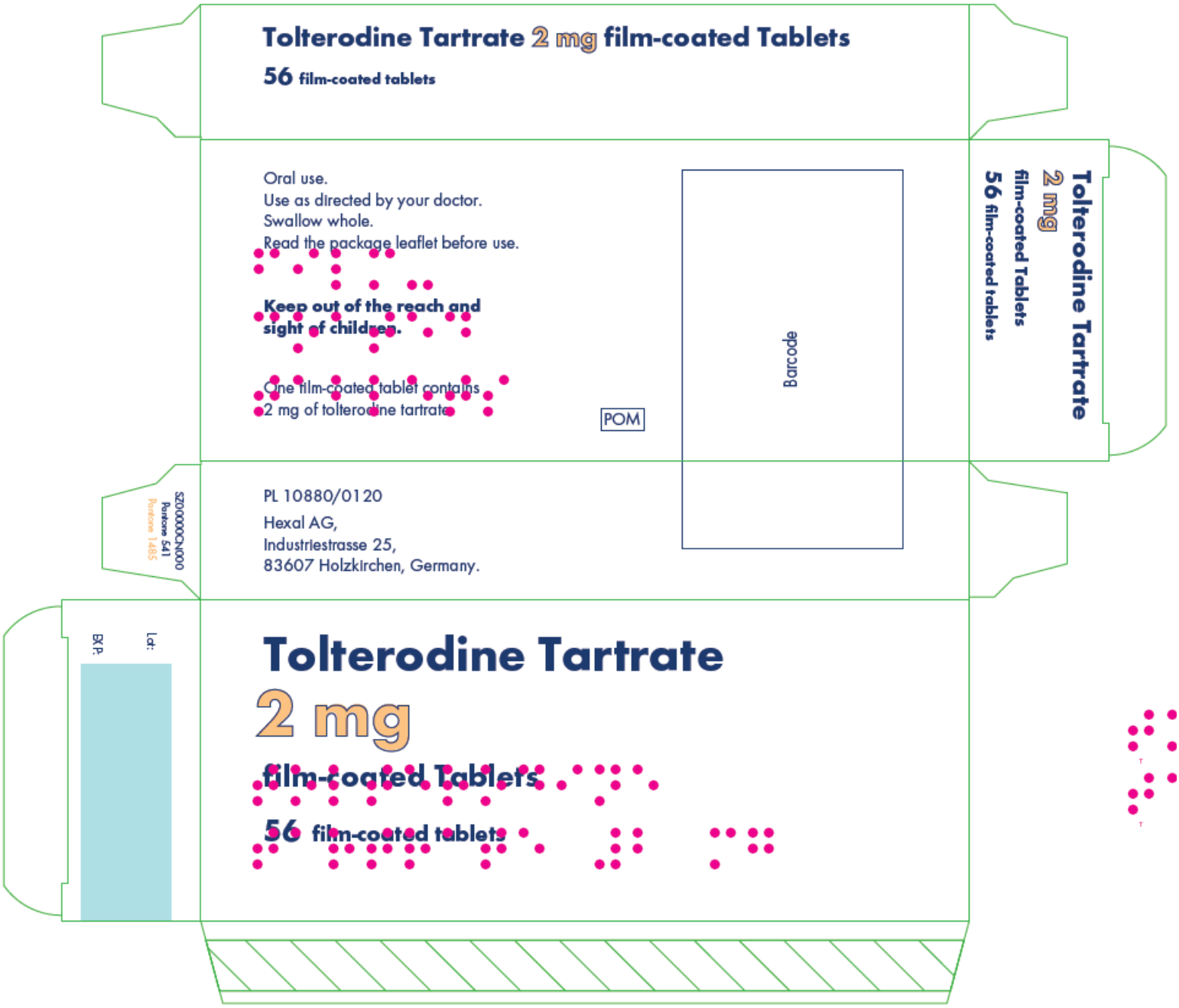
Marketing Authorisation Holder and Manufacturer
MA Holder:
Sandoz Ltd, 37 Woolmer Way, Bordon, Hampshire, GU35 9QE.
Manufacturer:
Salutas Pharma GmbH, Otto-von-Guericke- Allee 1, 39179 Barleben, Germany.

This leaflet was last approved in 02/2009
(to be completed after approval)

Module 4
Labelling






Tolterodine Tartrate 2 mg film-coated Tablets
56 film-coated tablets
Oral use.
Use as directed by your doctor.
Swallow whole.
Read the package leaflet before use.
Keep out of the reach and sight of children.
One film-coated tablet contains 2 mg of tolterodine tartrate
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Barcode
Tolterodine Tartrate
2 mg
film-coated Tablets
56 film-coated tablets
PL 10880/0120
Hexal AG,
Industriestrasse 25,
83607 Holzkirchen, Germany.
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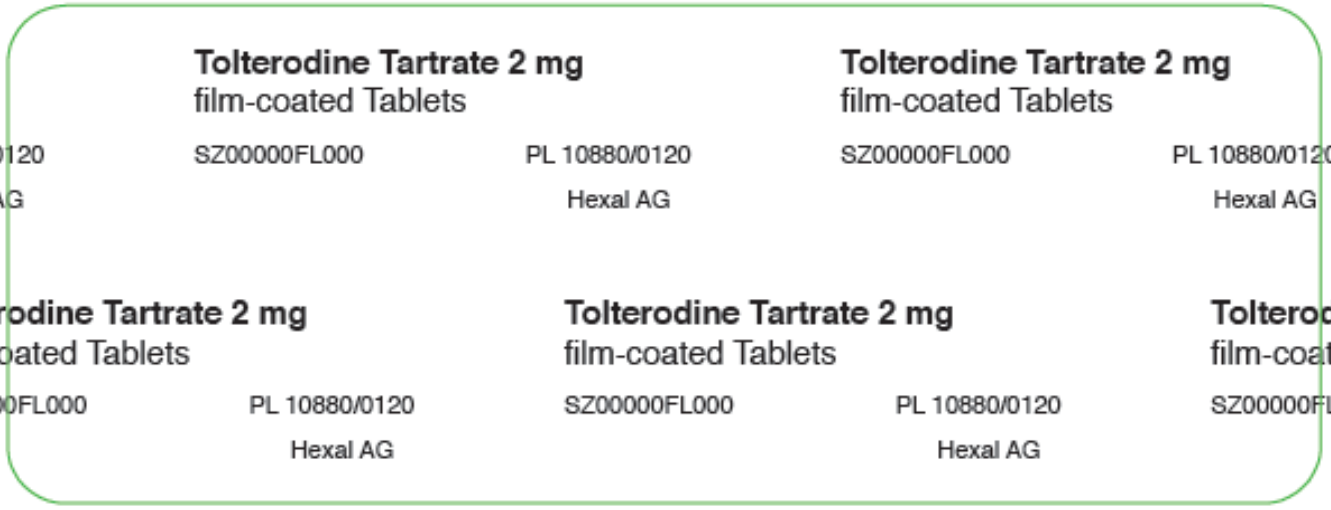
Lot:
Tolterodine Tartrate
2 mg
film-coated Tablets
56 film-coated tablets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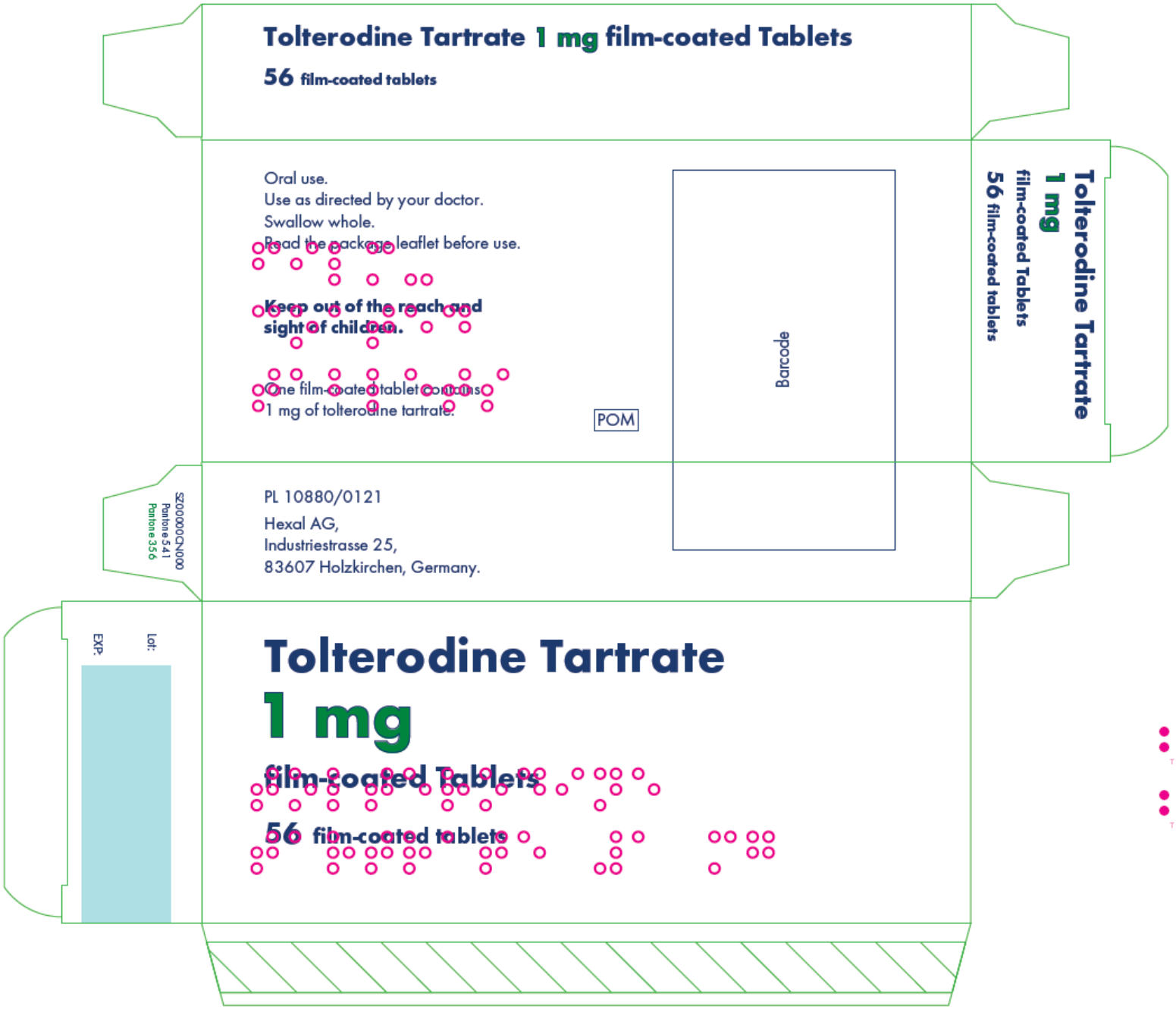
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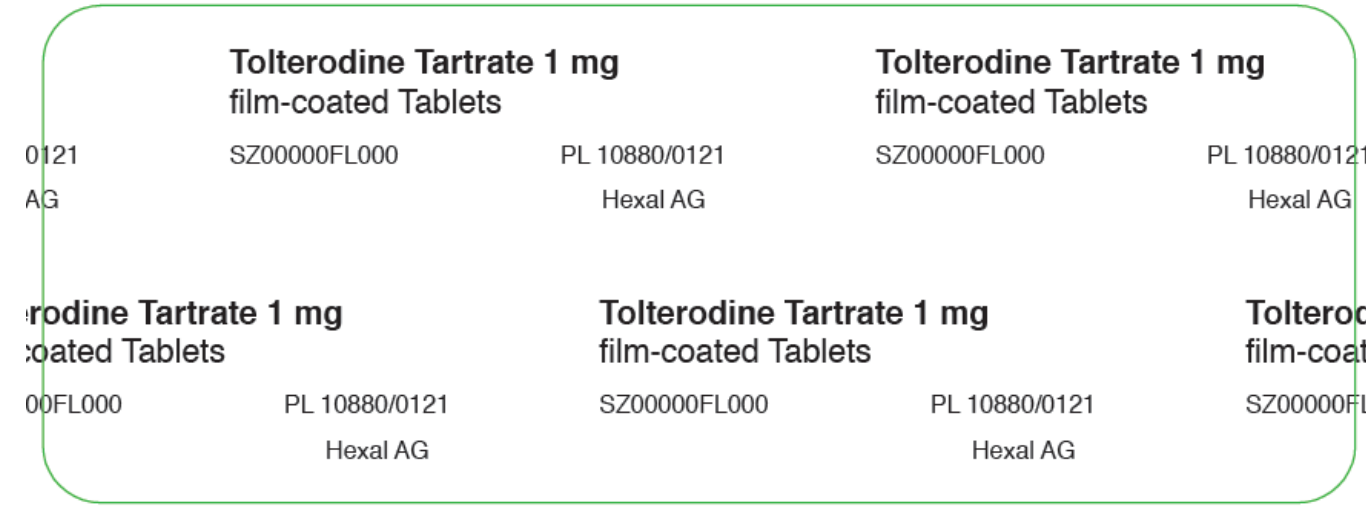
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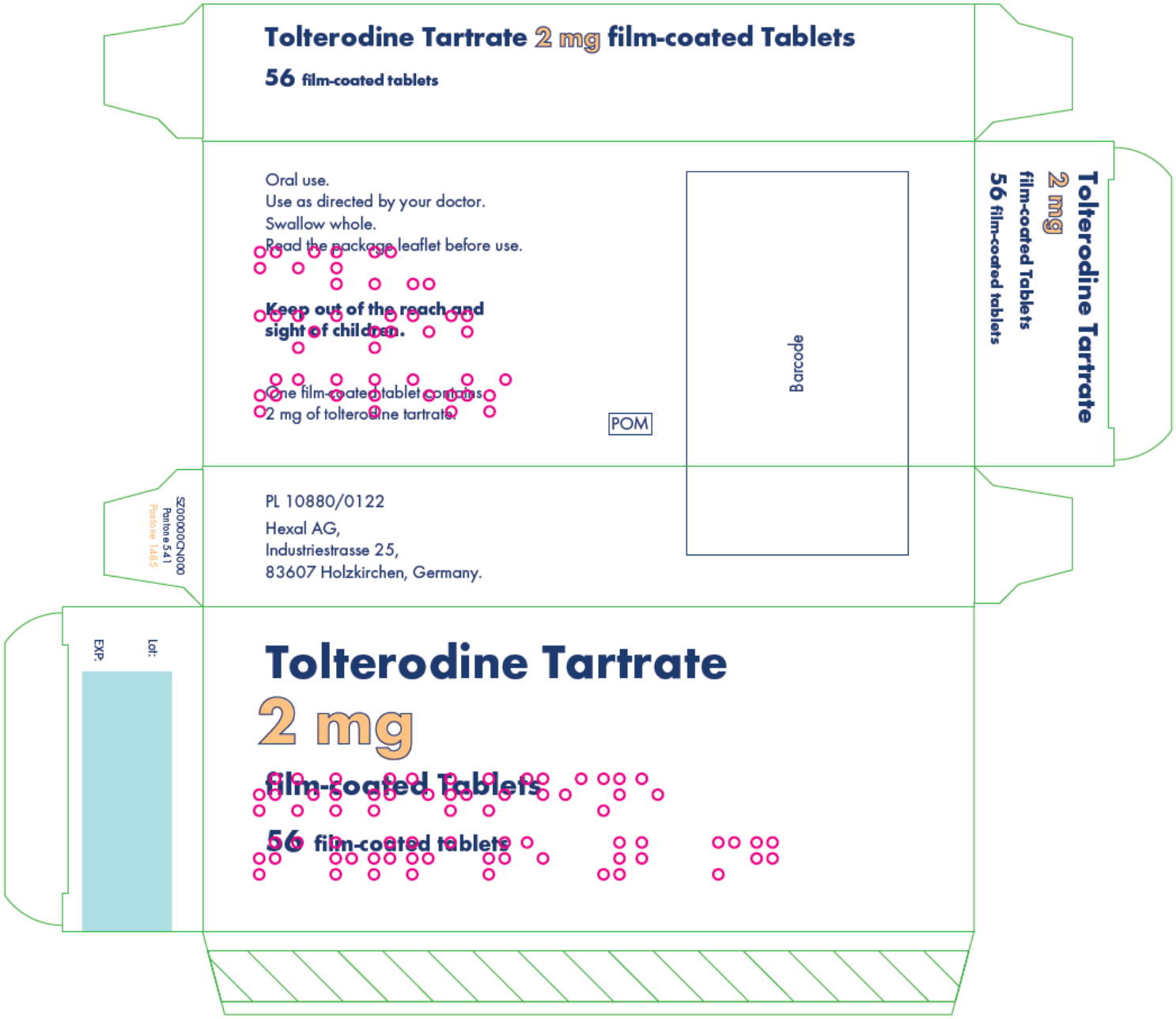
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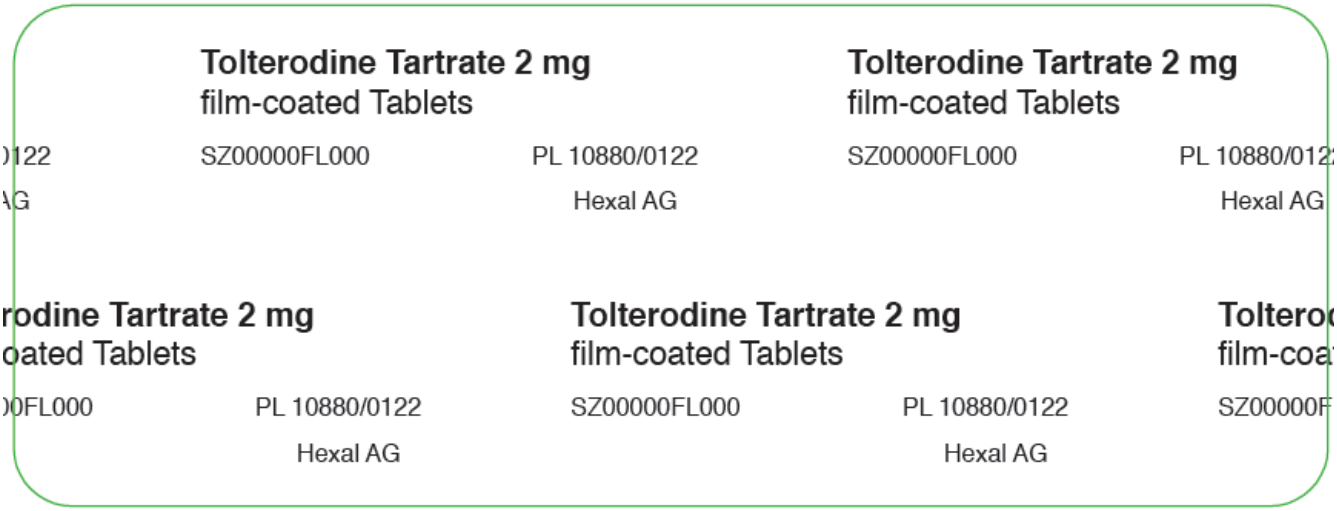
film-coated Tablets
56 film-coated tablets
PL 10880/0122
Hexal AG,
Industriestrasse 25,
83607 Holzkirchen, Germany.
SZ00000QN000
Pantone 541
Pantone 1485
EXP:
Lot:
Tolterodine Tartrate
2 mg
film-coated Tablets
56 film-coated tablets


Tolterodine Tartrate 2 mg
film-coated Tablets
SZ00000FL000
PL 10880/0122
Hexal AG
Tolterodine Tartrate 2 mg
film-coated Tablets
SZ00000FL000
PL 10880/0122
Hexal AG
Tolterodine Tartrate 2 mg
film-coated Tablets
SZ00000FL000
PL 10880/0122
Hexal AG
Tolterodine Tartrate 2 mg
film-coated Tablets
SZ00000FL000
PL 10880/0122
Hexal AG

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, Germany, Luxembourg, Spain and the UK considered that the applications for Tolterodine Tartrate 1mg and 2mg Film-Coated Tablets could be approved. These products are prescription only medicines (POM) for the symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder syndrome.

These applications for Tolterodine Tartrate 1mg and 2mg Film-Coated Tablets are submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal products to Detrusitol 1mg and 2mg Film-Coated Tablets, first authorised in the UK to Pharmacia Limited in February 1998.

The products contain the active substance tolterodine, 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.

No new preclinical studies were conducted, which is acceptable given that the products contain a widely-used, well-known active substance. No clinical studies with the exception of the bioequivalence study have been performed and none are required for these applications as the pharmacology of tolterodine is well-established.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Tolterodine Tartrate 1mg and 2mg Film-Coated Tablets
Name(s) of the active substance(s) (INN)	Tolterodine L-Tartrate
Pharmacotherapeutic classification (ATC code)	Urinary antispasmodics (G04B D07)
Pharmaceutical form and strength(s)	1mg and 2mg Film-Coated Tablets
Reference numbers for the Decentralised Procedure	UK/H/1375/001-2/DC; UK/H/1376/001-2/DC
Reference Member State	United Kingdom
Member States concerned	Germany, Luxembourg and Spain
Marketing Authorisation Number(s)	PL 10880/0119-122
Name and address of the authorisation holder	Hexal AG Industriestr. 25, 83607 Holzkirchen, Germany

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

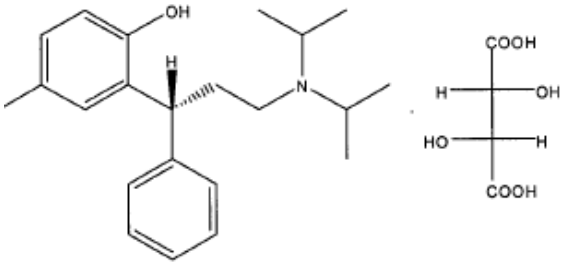
INN/Ph.Eur name: Tolterodine tartrate

Chemical name: (+)-N,N-diisopropyl-3-(2-hidroxy-5-methylphenyl)-3 phenylpropylamine-L-hydrogene tartrate

2-[(1R)-3-[Bis(l -methyl ethyl)amino]-1-phenyl propyl]-4-methyl phenol Tartrate

(+)-(R)-2-[α-[2-(diisopropylamino) ethyl] benzyl] -p-cresol tartrate

Structural formula:



Molecular formula: $C_{26}H_{37}NO_7$; $C_{22}H_{31}NO.\ C_4H_6O_6$

Appearance: White to off-white crystalline powder.

Solubility: Sparingly soluble in methanol, slightly soluble in ethanol, practically insoluble in toluene. Solubility water is 12 mg/ml.

Molecular weight: Tolterodine: 325.49 g/mol
Tolterodine Tartrate: 475.57 g/mol

Chirality: One chiral centre and exhibits enantiomerism. The drug substance is the (+) L-isomer.

Tolterodine tartrate complies with in-house specifications.

Synthesis of the drug 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.

All potential known impurities have been identified and characterised. Appropriate proof of structure data has been supplied for the active pharmaceutical ingredient.

An appropriate specification is provided for the active substance tolterodine tartrate, with suitable test methods and limits. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and certificates of analysis have been provided all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Suitable certificates of analysis have been provided for all reference standards used.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug, and supporting an appropriate retest period.

P. Medicinal Product

Other Ingredients

Other ingredients within the tablet core consist of pharmaceutical excipients calcium hydrogen phosphate-anhydrous, silica, microcrystalline cellulose, sodium starch glycolate (type A) and magnesium stearate. A declaration has been provided for magnesium stearate stating that it is sourced from vegetable origin.

The tablet film-coating layer contains hypromellose, microcrystalline cellulose, titanium dioxide and stearic acid. A declaration has been provided that states that the stearic acid used is produced from raw materials of non-animal origin
All excipients comply with their relevant European Pharmacopoeia monographs.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical Development

The objective of the development programme was to produce products that could be considered generic medicinal products of Detrusitol 1mg and 2mg Film-Coated Tablets (Pharmacia Limited).

The reference product used in the bioequivalence study is qualitatively and quantatively identical to the UK reference product.

The applicant has provided suitable product development sections. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative impurity profiles have been provided for the finished products versus the reference products of Detrusitol 1mg and 2mg Film-Coated Tablets (Pharmacia Limited).

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

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on three full scale batches per strength have been provided.

Finished Product Specification

The finished product specification proposed for the products is acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been

provided and comply with the release specifications. Certificates of analysis have been provided for any working standards used.

Container-Closure System
These products are packaged in either blister package made of aluminium and polyvinylchloride (PVC); aluminium, PVC and polyvinylidene chloride (PVDC) or plastic containers with high density polyethylene (HDPE) closures.
The product is packaged in blisters in sizes of 7, 14, 28, 30, 50, 56, 60, 84, 98 and 100 tablets and in bottles of 60 and 500 tablets.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary product packaging complies with EU legislation regarding contact with food.

Stability of the product
Stability studies were performed on batches of the finished products in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 30 months with no special storage instructions.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels
The SPCs, PILs and labelling are pharmaceutically acceptable.

User testing results have been submitted for typical PILs for these products. The results indicate that the PILs are 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 they contain.

MAA forms
The MAA forms are pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
It is recommended that Marketing Authorisations are granted for these applications.

III.2 PRE-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of tolterodine tartrate are well-known. As tolterodine tartrate is a widely used, well-known active substance, the applicant has not provided any additional studies and none are required.

The pre-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the pre-clinical aspects of the dossier.

III.3 CLINICAL ASPECTS

1. Introduction

This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier. For more details, the reader should refer to the company's clinical overview and summary and to the clinical file.

The clinical overview has been written by an appropriately qualified physician. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

2. Clinical study reports

To support these applications, the marketing authorisation holder has submitted one single dose bioequivalence study.

A single dose, randomised, two-sequence, two-period, crossover bioequivalence study of Tolterodine tartrate 2mg tablets versus Detrusitol 2mg tablets, (Pfizer Inc, Germany) in healthy, adult, human subjects under fasting conditions.

All subjects were in a fasted state before dosing. Blood sampling was performed pre- and up to 36 hours post dose in each treatment period. There was a washout period of 7 days. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results from this study are presented below as log-transformed values:

Treatment	AUC_{0-t} (ng/ml/h)	$AUC_{0-\infty}$ (ng/ml/h)	C_{max} (ng/ml)
Tolterodine Tartrate:			
Test	31087.5±8874.2	34815.0±10742.3	5111.4±732.0
Reference	28992.7±8052.3	33310.7±10255.3	4963.0±652.2
Ratio (90% CI)	96.8 – 113.1	96.5 – 112.6	89.9 – 110.2

Treatment	AUC_{0-t} (ng/ml/h)	$AUC_{0-\infty}$ (ng/ml/h)	C_{max} (ng/ml)
5-hydroxymethyl tolterodine:			
Test	14644.3±1100.0	14950.6±1093.2	2942.6±248.3
Reference	14781.9±1146.7	15119.8±1136.4	3187.3±274.4
Ratio (90% CI)	96.7 – 109.2	95.5 – 104.1	89.6 – 104.0

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC_{0-t} and C_{max} for tolterodine tartrate and metabolite, 5-hydroxymethyl tolterodine lie within 80-125% boundaries. Thus, bioequivalence has been shown between the test and reference products in this study.

As 1mg and 2mg strength products meet all the criteria as specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 2mg strength qualify for an extrapolation can be extrapolated to 1mg strength tablets also.

3. Post marketing experience

Tolterodine tartrate has a well-recognised efficacy and an acceptable level of safety in the indications approved for Detrusitol 1mg and 2mg Film-Coated Tablets and corresponding products have been widely used in many countries. Therefore, the submission of PSUR at the renewal of the marketing authorisations is supported.

4. Benefit-Risk assessment

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant's products and the innovator products are interchangeable. Extensive clinical experience with tolterodine tartrate is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

5. Conclusions

The grant of marketing authorisations for Tolterodine Tartrate 1mg and 2mg Film-Coated Tablets is recommended from a clinical viewpoint.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Tolterodine Tartrate 1mg and 2mg Film-Coated Tablets 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.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Tolterodine Tartrate 1mg and 2mg Film-Coated Tablets and the originator products Detrusitol 1mg and 2mg Film-Coated Tablets (Pharmacia Limited).

No new or unexpected safety concerns arise from these applications.

The SPCs, PILs and labelling are satisfactory and consistent with that for the innovator products.

RISK-BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with tolterodine tartrate is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Module 5

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome