SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tolthen XL 4 mg prolonged-release capsules, hard
Tolterodine Tartrate Northumbria 4mg prolonged-release capsules, hard

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect
Each 4 mg prolonged-release capsule, hard contains 65.408-68.992 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release capsule, hard

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Posology

Adults (including the elderly)
The recommended dose is 4 mg once daily except in patients with impaired liver function or severely impaired renal function (GFR $\leq$ 30 mL/min) for whom the recommended dose is 2 mg once daily (see sections 4.4 and 5.2). In case of troublesome and/or undesirable effects the dose may be reduced from 4 mg to 2 mg once daily.
The effect of treatment should be re-evaluated after 2-3 months (see section 5.1).

Paediatric population
The efficacy of tolterodine SR has not been demonstrated in children (see section 5.1). Therefore, Tolthen XL is not recommended for children.

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

4.3 Contraindications

Tolterodine is contraindicated in patients with:
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Urinary retention
- Uncontrolled narrow angle glaucoma

- Myasthenia gravis
- Severe ulcerative colitis
- Toxic megacolon.

4.4 Special warnings and precautions for use

Tolterodine shall be used with caution in patients with:
- Significant bladder outlet obstruction at risk of urinary retention
- Gastrointestinal obstructive disorders, e.g. pyloric stenosis
- Renal impairment (see sections 4.2 and 5.2)
- Hepatic disease (see sections 4.2 and 5.2)
- Autonomic neuropathy
- Hiatus hernia
- Risk of decreased gastrointestinal motility.

Multiple oral total daily doses of immediate release 4 mg (therapeutic) and 8 mg (supratherapeutic) tolterodine have been shown to prolong the QTc interval (see section 5.1). The clinical relevance of these findings is unclear and will depend on individual patient risk factors and susceptibilities present.

Tolterodine should be used with caution in patients with risk factors for QT prolongation including:
- Congenital or documented acquired QT prolongation
- Electrolyte disturbances such as hypokalemia, hypomagnesaemia and hypocalcaemia
- Bradycardia
- Relevant pre-existing cardiac diseases (i.e. cardiomyopathy, myocardial ischemia, arrhythmia, congestive heart failure)
- Concomitant administration of medicinal products known to prolong QT-interval including Class IA (e.g. quinidine, procainamide) and Class III (e.g. amiodarone, sotalol) anti-arrhythmics.

This especially holds true when taking potent CYP3A4 inhibitors (see section 5.1).

Concomitant treatment with potent CYP3A4 inhibitors should be avoided (see section 4.5, Interactions).

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

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
This medicinal product contains 0.00404 mmol (or 0.092988 mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant systemic medication with potent CYP3A4 inhibitors such as macrolide antibiotics (erythromycin and clarithromycin), antifungal agents (e.g. ketoconazole and itraconazole) and antiproteases is not recommended due to increased serum concentrations of tolterodine in poor CYP2D6 metabolisers with (subsequent) risk of overdose (see section 4.4).
Concomitant medication with other medicinal products that possess antimuscarinic properties may result in more pronounced therapeutic effect and undesirable effects. Conversely, the therapeutic effect of tolterodine may be reduced by concomitant administration of muscarinic cholinergic receptor agonists.
The effect of prokinetics like metoclopramide and cisapride may be decreased by tolterodine.
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 active substances metabolised by these isoenzymes is not expected when dosed in combination with tolterodine.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of tolterodine in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.
Consequently, tolterodine is not recommended during pregnancy.

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

Fertility
No data from fertility studies are available.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

System Organ Class	**Very Common** (≥ 1/10)	**Common** (≥ 1/100 to <1/10)	**Uncommon** (≥ 1/1,000 to <1/100)	**Not known** (cannot be estimated from the available data)
Infections and infestations		Sinusitis		
Immune system disorders			Hypersensitivity not otherwise specified	Anaphylactoid reactions
Psychiatric disorders			Nervousness	Confusion, hallucinations, disorientation
Nervous system disorders		Dizziness, somnolence, headache	Paraesthesia, memory impairment	
Eye disorders		Dry eyes, abnormal vision (including abnormal accommodation)		

Ear and labyrinth disorders			Vertigo	
Cardiac disorders			Palpitations, cardiac failure, arrhythmia	Tachycardia
Vascular disorders				Flushing
Gastrointestinal disorders	Dry mouth	Dyspepsia, constipation, abdominal pain, flatulence, diarrhoea		Gastroesophageal reflux, vomiting
Skin and subcutaneous tissue disorders				Angioedema, dry skin
Renal and urinary disorders		Dysuria	Urinary retention	
General disorders and administration site conditions		Fatigue, peripheral oedema	Chest pain	

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

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

The highest dose given to human volunteers of tolterodine tartrate is 12.8 mg as a single dose of the immediate release formulation. The most severe adverse events observed were accommodation disturbances and micturition difficulties.
In the event of tolterodine overdose, treat with gastric lavage and give activated charcoal. Treat symptoms as follows:
- Severe central anticholinergic effects (e.g. hallucinations, severe excitation): treat with physostigmine
- Convulsions or pronounced excitation: treat with benzodiazepines
- Respiratory insufficiency: treat with artificial respiration
- Tachycardia: treat with beta-blockers
- Urinary retention: treat with catheterisation
- Mydriasis: treat with pilocarpine eye drops and/or place patient in dark room

An increase in QT interval was observed at a total daily dose of 8 mg immediate release tolterodine (twice the recommended daily dose of the immediate release formulation and equivalent to three times the peak

exposure of the prolonged release capsule formulation) administered over four days. In the event of tolterodine overdose, standard supportive measures for managing QT prolongation should be adopted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Genito urinary system and sex hormones
Pharmacotherapeutic sub-group: Urinary antispasmodics
ATC Code: G04B D07

Tolterodine is a competitive, specific muscarinic receptor antagonist with a selectivity for the urinary bladder over salivary glands *in vivo*. One of the tolterodine metabolites (5-hydroxymethyl derivative) exhibits a pharmacological profile similar to that of the parent compound. In extensive metabolisers this metabolite contributes significantly to the therapeutic effect (see section 5.2).

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

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

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

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

**) 97.5% confidence interval according to Bonferroni*

After 12 weeks of treatment 23.8% (121/507) in the tolterodine SR 4 mg group and 15.7% (80/508) in the placebo group reported that they subjectively had no or minimal bladder problems.
The effect of tolterodine was evaluated in patients, examined with urodynamic assessment at baseline and, depending on the urodynamic result, they were allocated to a urodynamic positive (motor urgency) or a urodynamic negative (sensory urgency) group. Within each group, the patients were randomised to receive either tolterodine or placebo. The study could not provide convincing evidence that tolterodine had effects over placebo in patients with sensory urgency.
The clinical effects of tolterodine on QT interval were studied in ECGs obtained from over 600 treated patients, including the elderly and patients with pre-existing cardiovascular disease. The changes in QT intervals did not significantly differ between placebo and treatment groups.
The effect of tolterodine on QT-prolongation was investigated further in 48 healthy male and female volunteers aged 18 – 55 years. Subjects were administered 2 mg BID and 4 mg BID tolterodine as the immediate release formulations. The results (Fridericia corrected) at peak tolterodine concentration (1 hour)

showed mean QTc interval increases of 5.0 and 11.8 msec for tolterodine doses of 2 mg BID and 4 mg BID respectively and 19.3 msec for moxifloxacin (400 mg) which was used as an active internal control. A pharmacokinetic/pharmacodynamic model estimated that QTc interval increases in poor metabolisers (devoid of CYP2D6) treated with tolterodine 2 mg BID are comparable to those observed in extensive metabolisers receiving 4 mg BID. At both doses of tolterodine, no subject, irrespective of their metabolic profile, exceeded 500 msec for absolute QTcF or 60 msec for change from baseline that are considered thresholds of particular concern. The 4 mg BID dose corresponds to a peak exposure (C_{max}) of three times that obtained with the highest therapeutic dose of tolterodine SR 4 mg capsules.

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

5.2 Pharmacokinetic properties

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

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

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

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

Elimination
Tolterodine is extensively metabolised by the liver following oral dosing. The primary metabolic route is mediated by the polymorphic enzyme CYP2D6 and leads to the formation of the 5-hydroxymethyl metabolite. Further metabolism leads to formation of the 5-carboxylic acid and N-dealkylated 5-carboxylic acid metabolites, which account for 51 % and 29 % of the metabolites recovered in the urine, respectively. A subset (about 7%) of the population is devoid of CYP2D6 activity. The identified pathway of metabolism for these individuals (poor metabolisers) is dealkylation via CYP3A4 to N-dealkylated tolterodine, which does not contribute to the clinical effect. The remainder of the population is referred to as extensive metabolisers. The systemic clearance of tolterodine in extensive metabolisers is about 30 L/h. In poor metabolisers the reduced clearance leads to significantly higher serum concentrations of tolterodine (about 7-fold) and negligible concentrations of the 5-hydroxymethyl metabolite are observed.
The 5-hydroxymethyl metabolite is pharmacologically active and equipotent with tolterodine. Because of the differences in the protein-binding characteristics of tolterodine and the 5-hydroxymethyl metabolite, the exposure (AUC) of unbound tolterodine in poor metabolisers is similar to the combined exposure of unbound tolterodine and the 5-hydroxymethyl metabolite in patients with CYP2D6 activity given the same dose 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 active substance, 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 dose range.

Specific patient groups

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

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

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

5.3 Preclinical safety data

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

Reproduction studies have been performed in mice and rabbits.

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

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

Tolterodine, as well as its active human metabolites prolong action potential duration (90 % repolarisation) in canine purkinje fibres (14 - 75 times therapeutic levels) and block the K^+-current in cloned human ether-a-go-go-related gene (hERG) channels (0.5 – 26.1 times therapeutic levels). In dogs prolongation of the QT interval has been observed after application of tolterodine and its human metabolites (3.1 – 61.0 times therapeutic levels). The clinical relevance of these findings is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Cellulose microcrystalline

Poly(vinyl acetate)
Povidone
Silica
Sodium laurilsulfate
Sodium docusate

Magnesium stearate
Hydroxypropylmethylcellulose

Capsule composition:
- Indigo carmine (E132)
- Titanium dioxide (E171)
- Gelatin
- Quinoline yellow (E104) (only in 2mg)

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years
HDPE bottle: Shelf life after first opening is 200 days

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

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

Pack sizes for 4 mg capsules:
Blister packs containing: 7, 14, 28, 49, 84, 98 prolonged-release hard capsules

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

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