SCHEDULING STATUS: S3

PROPRIETARY NAME (AND DOSAGE FORM):

DETRUSITOL® SR 2 mg Prolonged release capsules

DETRUSITOL® SR 4 mg Prolonged release capsules

COMPOSITION:

DETRUSITOL SR 2 mg capsules contain 2 mg tolterodine L-tartrate.

DETRUSITOL SR 4 mg capsules contain 4 mg tolterodine L-tartrate.

Contains sugar:

Each DETRUSITOL SR 2 mg capsule contains 67,23 mg sucrose.

Each DETRUSITOL SR 4 mg capsule contains 134,5 mg sucrose.

The other inactive ingredients are ethylcellulose, hydroxypropyl methylcellulose, medium chain triglycerides and oleic acid. The capsules contain gelatine, titanium dioxide (E171), colourants FD&C Blue #2 (2 mg and 4 mg capsules) and Yellow Iron Oxide (E 172) (2 mg capsules only). The printing ink also contains shellac glaze, propylene glycol and simethicone.

PHARMACOLOGICAL CLASSIFICATION:

A 5.4 Cholinolytics (anticholinergics)

PHARMACOLOGICAL ACTION:

Tolterodine is a competitive muscarinic receptor antagonist which in animal studies exhibits a selectivity for the urinary bladder over salivary glands. The clinical significance of this is not established.

After oral administration, tolterodine is metabolised in the liver mainly by the cytochrome P450 2D6 enzyme, resulting in the formation of the 5-hydroxymethyl metabolite.

In extensive metabolisers the 5-hydroxymethyl metabolite is a major pharmacologically active metabolite with a pharmacological profile similar to that of the parent compound.

This metabolite contributes significantly to the therapeutic effect of tolterodine. Both tolterodine and its metabolite show a high specificity for muscarinic receptors.

Pharmacokinetics:

Both tolterodine and the 5-hydroxymethyl metabolite reach maximum serum concentrations 2 – 6 hours after administration of a 4 mg tolterodine prolonged release capsule. The pharmacokinetics is linear in the therapeutic dosage range. Tolterodine is mainly metabolised by the polymorphic enzyme CYP2D6 leading to the formation of a pharmacologically active 5-hydroxymethyl metabolite. The systemic serum clearance of tolterodine in extensive metabolisers is about 30 L/h.

The half-life for tolterodine given as the prolonged release capsule is approximately 6 hours and the half-life of the 5-hydroxymethyl metabolite is the same. In poor metabolisers (deficient of CYP2D6) tolterodine is dealkylated via CYP3A isoenzymes whereby N-dealkylated tolterodine is formed which does not contribute to the clinical effect. After administration of tolterodine 4 mg prolonged release capsules the half-life of tolterodine is approximately 11 hours in poor metabolisers.

The reduced clearance of the parent compound in poor metabolisers leads to increased concentrations of tolterodine (about 7-fold) associated with undetectable concentrations of the 5-hydroxymethyl metabolite. As a result, 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. Steady state concentrations are reached within 4 days after administration of tolterodine 4 mg prolonged release capsules.

The absolute bioavailability of tolterodine is 65 % in poor metabolisers (devoid of CYP2D6) and 17 % in extensive metabolisers.

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. The excretion of radioactivity after administration of [^{14}C]- tolterodine is approximately 77 % in urine and 17 % in faeces. Less than 1 % of the dose is excreted 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. About 2-fold higher exposure of unbound tolterodine and the 5-hydroxymethyl metabolite is found in liver cirrhosis subjects.

INDICATIONS:

DETRUSITOL SR capsules are indicated for the treatment of overactive bladder with symptoms of urinary urgency, frequency and/or urge incontinence.

CONTRAINDICATIONS:

DETRUSITOL SR is contraindicated in patients with:

- Known hypersensitivity to tolterodine or excipients.
- Urinary retention.
- Gastric retention.
- Uncontrolled narrow angle glaucoma.
- Myasthenia gravis.
- Severe ulcerative colitis.
- Toxic megacolon.

Safety and efficacy in children have not yet been established.

WARNINGS:

DETRUSITOL SR should be used with caution in the following patients:

- At risk of urinary retention.
- Controlled narrow angle glaucoma.
- At risk of decreased gastrointestinal motility obstructive disorders e.g. pyloric stenosis.
- With impaired renal function.
- With impaired hepatic function.
- With myasthenia gravis.
- Autonomic neuropathy.
- Hiatus hernia.

Organic causes for urgency, frequency and/or urge incontinence should be excluded before considering treatment with DETRUSITOL SR.

INTERACTIONS:

Concomitant medication with other medicines that possess anticholinergic properties may result in more

pronounced therapeutic effect and side effects. Conversely, the therapeutic effect of DETRUSITOL SR capsules may be reduced by concomitant administration of cholinergic receptor agonists. The effects of prokinetics like metoclopramide and cisapride may be decreased by DETRUSITOL SR capsules.

Pharmacokinetic interaction is possible with other drugs metabolised by or inhibiting cytochrome P450 2D6 e.g. fluoxetine. Concomitant treatment with fluoxetine results in a 25 % increase in the combined exposure of unbound DETRUSITOL SR capsules and the equipotent metabolite. No dosage adjustment is usually required.

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

Patients on concomitant medication with potent cytochrome P4503A4 inhibitors e.g. macrolide antibiotics (erythromycin and clarithromycin) or azole antifungal agents (e.g. ketoconazole, itraconazole and miconazole) should be treated with caution. Ketoconazole, a potent inhibitor of cytochrome P4503A4, significantly increased plasma concentrations of tolterodine when co-administered to poor metabolisers (i.e. patients devoid of cytochrome P4502D6 metabolic pathway) (see DOSAGE AND DIRECTIONS FOR USE).

Prolongation of the QTc interval has occurred and should be considered in patients who are taking Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic medications.

No interaction with warfarin or combined oral contraceptives (ethinyl oestradiol/ levonorgestrel) occurs.

Co-administration with diuretic agents (indapamide, hydrochlorothiazide, triamterene or furosemide) does not cause any adverse ECG effects.

PREGNANCY AND LACTATION:

The safety of this medicine has not been established in pregnant and breastfeeding women.

Women of childbearing potential should be advised to ensure adequate contraceptive cover.

DOSAGE AND DIRECTIONS FOR USE:

DETRUSITOL SR 2 mg and 4 mg capsules can be taken with or without food and must be swallowed whole.

Adults:

The recommended dose is 4 mg once daily. The total daily dose may be reduced to 2 mg, based on individual tolerability.

Use in impaired renal or hepatic function:

The recommended dose is 2 mg once daily.

For patients receiving ketoconazole or other potent cytochrome P4503A4 inhibitors, the recommended daily dose is 2 mg.

After 6 months of treatment, the need for further treatment should be reconsidered.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Side effects:

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

The side effects reported in clinical trials were categorised utilising the incidence rate as follows: Very common: ≥ 1/10 (≥ 10 %); Common: ≥ 1/100 and < 1/10 (≥ 1 % and < 10 %); Uncommon: ≥ 1/1 000 and < 1/100 (≥ 0,1 % and < 1 %); Rare: ≥ 1/10 000 and < 1/1 000 (≥ 0,01 % and < 0,1 %).

System Organ Class	**Frequency**	**Adverse events**
Infections and infestations	Common	Bronchitis, sinusitis
Immune system disorders	Uncommon	Allergic reactions
Psychiatric disorders	Uncommon	Confusion
Nervous system disorders	Common	Dizziness, headache, somnolence
Eye disorders	Common	Abnormal vision (including abnormal accommodation), dry eyes (reduced lacrimation)
Ear and labyrinth disorders	Common	Vertigo
Vascular disorders	Uncommon	Flushed skin
Gastrointestinal disorders	Very common	Dry mouth
	Common	Abdominal pain, constipation, dyspepsia, flatulence
	Uncommon	Gastroesophageal reflux

Skin and subcutaneous tissue disorders	Common	Dry skin
Renal and urinary disorders	Common	Dysuria
	Uncommon	Urinary retention
General disorders and administration site conditions	Common	Chest pain, fatigue
Investigations	Common	Increased weight

The following side effects were reported during post-marketing surveillance:

Immune system disorders: Anaphylactoid reactions.

Psychiatric disorders: Disorientation, hallucinations.

Nervous system disorders: Memory impairment.

Cardiac disorders: Tachycardia, palpitations.

Gastrointestinal disorders: Diarrhoea.

Skin and subcutaneous tissue disorders: Angioedema.

General disorders and administration site conditions: Peripheral oedema.

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

Special precautions:

General:

Risk of urinary retention and gastric retention: DETRUSITOL SR capsules should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention and to patients with gastrointestinal obstructive disorders, such as pyloric stenosis, because of the risk of gastric retention (see CONTRAINDICATIONS).

Controlled narrow-angle glaucoma: DETRUSITOL SR capsules should be used with caution in patients being treated for narrow-angle glaucoma.

Reduced hepatic and renal function: Patients with significantly reduced hepatic function and impaired renal function should not receive doses of DETRUSITOL SR capsules greater than 2 mg daily. Patients

with renal impairment should be treated with caution.

Prolongation of the QTc interval has occurred in controlled studies using both therapeutic and higher doses of DETRUSITOL SR. These observations should be considered in clinical decisions to prescribe DETRUSITOL SR for patients with:

- Congenital or documented acquired QT prolongation.
- Patients who are taking Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic medications.

Effects on ability to drive and use machines:

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

The most severe adverse events observed were accommodation disturbances and micturition difficulties.

Overdosage with DETRUSITOL SR capsules can potentially result in severe central antimuscarinic effects and should be treated accordingly.

In the event of an overdose, treat with gastric lavage and give activated charcoal.

Standard supportive measures for managing QT prolongation should be adopted.

Treat the symptoms/signs as follows:

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

IDENTIFICATION:

DETRUSITOL SR 2 mg: Blue-green capsules with white printing (figurine and 2) containing multi-layer

white film-coated beads.

DETRUSITOL SR 4 mg: Blue capsules with white printing (figurine and 4) containing multi-layer white film-coated beads.

PRESENTATION:

DETRUSITOL SR capsules are available in white HDPE bottles each containing 30, 90 or 500 capsules or clear, colourless, PVC/PVDC film and aluminium foil blister strips containing either 7 or 14 capsules. Each strip is packed into an outer carton which may contain either 7, 28, 49, 84 or 280 capsules.

STORAGE INSTRUCTIONS:

Store at or below 25 °C.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

DETRUSITOL SR 2 mg: 36/5.4/0448

DETRUSITOL SR 4 mg: 36/5.4/0449

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE REGISTRATION CERTIFICATE:

Viatris Healthcare (Pty) Ltd

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Manufacturer: Catalent Pharma Solutions, LLC, Kentucky, USA

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09 September 2009

BOTSWANA: S2

DETRUSITOL SR 2 mg – Reg. No.: BOT0801410

DETRUSITOL SR 4 mg – Reg. No.: BOT0801411

NAMIBIA: NS2

DETRUSITOL SR 2 mg – Reg. No.: 04/5.4/2084

DETRUSITOL SR 4 mg – Reg. No.: 04/5.4/2085