1. NAME OF THE MEDICINAL PRODUCT

TOLTERODINE MEVON SR CAPSULE 2 MG
TOLTERODINE MEVON SR CAPSULE 4 MG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One prolonged-release capsule, hard contains 2 mg of tolterodine tartrate, which is equivalent to 1.37 mg of tolterodine.
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 2 mg prolonged-release capsule, hard contains 32.704-34.496 mg lactose monohydrate.
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

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

Tolterodine is indicated for the treatment of overactive bladder with symptoms of urinary urgency, frequency, and/or urge incontinence.

4.2 Posology and method of administration

The extended-release capsules can be taken with or without food and must be swallowed whole **(see Section 5.2 – Pharmacokinetic Properties, Pharmacokinetic characteristics).**

Adults (including the Elderly)
The recommended total daily dose is 4 mg. Dosage with tolterodine capsules is 4 mg once daily. The total daily dose may be reduced to 2 mg, based on individual tolerability.

Use in Children
Safety and effectiveness in children have not yet been established.

Use in Impaired Renal Function
The recommended total daily dose is 2 mg (i.e., tolterodine capsules 2 mg once daily) for patients with impaired renal function **(see Section 4.4 – Special Warnings and Precautions for Use).**

Use in Impaired Hepatic Function
The recommended total daily dose is 2 mg (i.e., tolterodine capsules 2 mg once daily) for patients with impaired hepatic function **(see Section 4.4 – Special Warnings and Precautions for Use).**

Use with Potent CYP3A4 Inhibitors
The recommended total daily dose is 2 mg (i.e., tolterodine capsules 2 mg once daily) for patients receiving concomitant ketoconazole or other potent CYP3A4 inhibitors **(see Section 4.4 – Special Warnings and Precautions for Use, CYP3A4 inhibitors, and Section 4.5 – Interactions with Other Medicinal Products and Other Forms of Interaction).**

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

4.4 Special Warnings And Precautions For Use

Tolterodine should be used with caution in the following patients
– At risk for urinary retention
– At risk for decreased gastrointestinal motility
- With impaired renal function **(see Section 4.2 – Posology and Method of Administration, Use in Impaired Renal Function, and Section 5.2 – Pharmacokinetic Properties, Specific patient groups)**
– With impaired hepatic function **(see Section 4.2- Posology and Method of Administration, Use in Impaired Hepatic Function and Section 5.2 Pharmacokinetic Properties, Specific patient groups)**
– With myasthenia gravis

In a study of the effect of tolterodine immediate- release tablets on the QT interval, the effect on the QT interval appeared greater for 8 mg/day (two times the therapeutic dose) compared to 4 mg/day and was more pronounced in CYP2D6 poor metabolizers (PM) than extensive metabolizers (EMs) **(see Section 5.1 – Pharmacodynamic Properties).**
The effect of tolterodine 8 mg/day was not as large as that observed after four days of therapeutic dosing with the active control moxifloxacin. However, the confidence intervals overlapped.

These observations should be considered in clinical decisions to prescribe tolterodine extended-release capsules 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

CYP3A4 inhibitors
The recommended total daily dose of tolterodine is 2 mg for patients on concomitant medication with potent CYP3A4 inhibitors, such as macrolide antibiotics (e.g., erythromycin and clarithromycin) or azole antifungal agents (e.g., ketoconazole, itraconazole and miconazole) **(see Section 4.2 – Posology and Method of Administration, Use with Potent CYP3A4 Inhibitors, and Section 4.5 – Interactions with Other Medicinal Products and Other Forms of Interaction).**

4.5 Interaction With Other Medicinal Products And Other Forms Of Interaction

Pharmacokinetic interactions are possible with other drugs metabolized by or inhibiting cytochrome P450 2D6 (CYP2D6) or CYP3A4. Concomitant treatment with fluoxetine does not result in a clinically significant interaction.
Ketoconazole, a potent inhibitor of CYP3A4, significantly increased plasma concentrations of tolterodine when coadministered to poor metabolizers (ie. persons devoid of CYP2D6 metabolic pathway). For patients receiving ketoconazole or other potent CYP3A4 inhibitors, the recommended total daily dose is 2mg **(see section 4.2 – Posology and Method of Administration, Use with Potent CYP3A4 Inhibitors, and Section 4.4 – Special Warnings and Precautions for Use, CYP3A4 inhibitors).**
Clinical studies have shown no interactions with warfarin or combined oral contraceptives (ethinyl estradiol/levonorgestrel).
A clinical study with marker drugs for major P450 isoenzymes has not shown any evidence that the activity

of CYP2D6, 2C19, 2C9, 3A4 or 1A2 will be inhibited by tolterodine.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no studies in pregnant women. Therefore, tolterodine should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Lactation
Use of tolterodine during lactation should be avoided since no data on excretion into breast milk in humans are available.

4.7 Effects on ability to drive and use machines

The ability to drive and use machinery may be negatively affected. Patients should be advised to exercise caution.

4.8 Undesirable effects

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

Clinical Trials: Adverse events considered potentially drug-related from studies of tolterodine capsules are provided below.

Infections and Infestations: sinusitis
Immune System Disorders: allergic reactions
Psychiatric Disorders: confusion
Nervous System Disorders: dizziness, headache, somnolence
Eye Disorders: abnormal vision (including abnormal accommodation), dry eyes
Ear and Labyrinth Disorders: vertigo
Vascular Disorders: flushed skin
Gastrointestinal Disorders: dry mouth, abdominal pain, constipation, dyspepsia, flatulence, gastroesophageal reflux
Renal and Urinary Disorders: dysuria, urinary retention
General Disorders and Administration Site Conditions: fatigue

The following adverse events 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: diarrhea
Skin and Subcutaneous Tissue Disorders: angioedema
General Disorders and Administration Site Conditions: peripheral edema

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.

4.9 Overdose

The highest dose of tolterodine given to human volunteers was 12.8 mg as single dose. The most severe adverse events observed were accommodation disturbances and micturition difficulties.

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

In the event of tolterodine overdose, standard supportive measures for managing QT prolongation should be adopted (**see Section 4.4 – Special Warnings and Precautions for Use, and Section 5.1 – Pharmacodynamic Properties**).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 metabolizers this metabolite contributes significantly to the therapeutic effect **(see Section 5.2 – Pharmacokinetic Properties, Metabolism)**.

Effect of the treatment can be expected within 4 weeks.

A total of 710 pediatric patients (486 on tolterodine extended-release capsules, 224 on placebo) aged 5-10 with urinary frequency and urge incontinence were studied in two phase 3 randomized, placebo-controlled, double-blind, 12-week studies. The percentage of patients with urinary tract infections was higher in patients treated with tolterodine extended-release capsules (6.6%) compared to patients who received placebo (4.5%). Aggressive, abnormal and hyperactive behavior and attention disorders occurred in 2.9% of children treated with tolterodine extended-release capsules compared to 0.9% of children treated with placebo.

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.

Table 1*: Effect of treatment with tolterodine extended-release 4 mg once daily after 12 weeks, compared with placebo. Absolute change and percentage change relative to baseline. Treatment difference tolterodine extended-release vs. placebo: Least Squares estimated mean change and 95% confidence interval.*

	Tolterodine extended-release 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 extended-release 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 randomized 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 effect of 2 mg BID and 4 mg BID of tolterodine immediate-release (tolterodine IR) tablets on the QT interval was evaluated in a 4-way crossover, double-blind, placebo- and active-controlled (moxifloxacin 400 mg QD) study in healthy male (N=25) and female (N=23) volunteers aged 18-55 years. There was an approximately equal representation of CYP2D6 extensive metabolizers (EMs) and poor metabolizers (PMs). The 4 mg BID dose of tolterodine IR (two times the highest recommended dose) was chosen because this dose results in tolterodine exposure similar to that observed upon co-administration of tolterodine 2 mg BID with potent CYP3A4 inhibitors in patients who are CYP2D6 poor metabolizers **(see Section 4.4 – Special Warnings and Precautions for Use, and Section 4.9 – Overdose)**.

Table 2 summarizes the mean change from baseline to steady state in corrected QT interval (Fridericia's QTcF and population-specific QTcP) relative to placebo at the time of peak tolterodine (1 hour) and moxifloxacin (2 hour) concentrations. QT interval was measured manually and by machine, and data from both are presented. The reason for the difference between machine and manual read of QT interval is unclear.

Table 2*: Mean (CI) change in QTc from baseline to steady state (Day 4 of dosing) at Tmax (relative to placebo)*

Drug/Dose	**N**	**QTcF (msec) (manual)**	**QTcF (msec) (machine)**	**QTcP (msec) (manual)**	**QTcP (msec) (machine)**
Tolterodine 2 mg BID[1]	48	5.01 (0.28, 9.74)	1.16 (-2.99, 5.30)	4.45 (-0.37, 9.26)	2.00 (-1.81, 5.81)
Tolterodine 4 mg BID[1]	48	11.84 (7.11, 16.58)	5.63 (1.48, 9.77)	10.31 (5.49, 15.12)	8.34 (4.53, 12.15)
Moxifloxacin 400 mg QD[2]	45	19.263 (15.49, 23.03)	8.90 (4.77, 13.03)	19.103 (15.32, 22.89)	9.29 (5.34, 13.24)

[1] At T_{max} of 1 hr; 95% Confidence Interval
[2] At T_{max} of 2 hr; 90% Confidence Interval
[3] The effect on QT interval with 4 days of moxifloxacin dosing in this QT trial may be greater than typically observed in QT trials.

The QT effect of tolterodine immediate-release tablets appeared greater for 8 mg/day (two times the therapeutic dose) compared to 4 mg/day. The effect of tolterodine 8 mg/day was not as large as that observed after four days of therapeutic dosing with the active control moxifloxacin.

There appeared to be a greater QTc interval increase in PMs than in EMs after tolterodine treatment in this study **(see Section 4.4 – Special Warnings and Precautions for Use, and Section 4.9 – Overdose)**.

5.2 Pharmacokinetic properties

Pharmacokinetic characteristics
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 alpha-1 acid-glycoprotein. The unbound fractions are 3.7% and 36%, respectively. The volume of distribution of tolterodine is 113 L.

Metabolism
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.

Excretion
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 dose range.

Specific patient groups

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

5.3 Preclinical safety data

In toxicity, genotoxicity and carcinogenicity 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 (23 – 123 times therapeutic levels) and block the K^+-current in cloned human ether-a-go-go-related gene (hERG) channels (0.8 – 14.7 times therapeutic levels). In dogs prolongation of the QT interval has been observed after application of tolterodine and its human metabolites (5.1 – 62.7 times therapeutic levels).

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)
- Quinoline yellow (only in 2 mg) (E104)
- Titanium dioxide (E171)
- Gelatin

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

Refer to outer carton or blisters for expiry date.

6.4 Special precautions for storage

Store at or below 30 °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 2 mg and 4 mg capsules:
Box of 30 prolonged-release hard capsules in blister packs

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. PRODUCT REGISTRANT

Novem Pharma Pte Ltd
23 New Industrial Road
Solstice Business Center #03-08
Singapore 536209

8. DATE OF REVISION OF THE TEXT

Jan 2022