HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Detrol® LA safely and effectively. See full prescribing information for Detrol LA.

Detrol® LA (tolterodine tartrate extended release capsules)
For oral administration
Initial U.S. Approval: December 2000

----------RECENT MAJOR CHANGES----------

Contraindications: Hypersensitivity to fesoterodine fumarate (4)	09/2011
Warnings and Precautions: Angioedema (5.1)	09/2011
Warnings and Precautions: Central Nervous System Effects (5.5)	08/2012

----------INDICATIONS AND USAGE----------

DETROL LA is an antimuscarinic indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. (1)

----------DOSAGE AND ADMINISTRATION----------

- 4 mg capsules taken orally once daily with water and swallowed whole. (2.1)
- 2 mg capsules taken orally once daily with water and swallowed whole in the presence of:
  - mild to moderate hepatic impairment (Child-Pugh class A or B) (2.2)
  - severe renal impairment [Creatinine Clearance (CCr) 10-30 mL/min] (2.2)
  - drugs that are potent CYP3A4 inhibitors. (2.2)
- DETROL LA is not recommended for use in patients with CCr <10 mL/min. (2.2)
- DETROL LA is not recommended for use in patients with severe hepatic impairment (Child-Pugh Class C). (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 2 mg and 4 mg (3)

---------- CONTRAINDICATIONS----------

DETROL LA is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma. DETROL LA is also contraindicated in patients with known hypersensitivity to the drug or its ingredients, or to fesoterodine fumarate extended-release tablets which, like DETROL LA, are metabolized to 5-hydroxymethyl tolterodine. (4)

----------WARNINGS AND PRECAUTIONS----------

- Anaphylaxis and angioedema requiring hospitalization and emergency medical treatment have occurred with the first or subsequent doses of DETROL LA. (5.1)
- Urinary Retention: use caution in patients with clinically significant bladder outflow obstruction because of the risk of urinary retention. (5.2)
- Gastrointestinal Disorders: use caution in patients with gastrointestinal obstructive disorders or decreased gastrointestinal motility because of the risk of gastric retention. (5.3)
- Controlled Narrow-Angle Glaucoma: use caution in patients being treated for narrow-angle glaucoma. (5.4)
- Central Nervous System Effects: Somnolence has been reported with Detrol LA. Advise patients not to drive or operate heavy machinery until they know how Detrol LA affects them (5.5).
- Myasthenia Gravis: use caution in patients with myasthenia gravis. (5.8)
- QT Prolongation**:** consider observations from the thorough QT study in clinical decisions to prescribe DETROL LA to patients with a known history of QT prolongation or to patients who are taking Class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications. (5.9)

----------ADVERSE REACTIONS----------

The most common adverse reactions (incidence ≥4% and >placebo) were dry mouth, headache, constipation, and abdominal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc at 1-800-438-1985 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- Potent CYP3A4 Inhibitors: Coadministration may increase systemic exposure to DETROL LA. Reduce DETROL LA dose to 2 mg once daily. (7.2)
- Other Anticholinergics (antimuscarinics): Concomitant use with other anticholinergic agents may increase the frequency and/or severity of dry mouth, constipation, blurred vision, and other anticholinergic pharmacological effects. (7.6)

----------USE IN SPECIFIC POPULATIONS----------

- *Pregnancy and Lactation:* DETROL LA should be used during pregnancy only if the potential benefit for the mother justifies the potential risk to the fetus. DETROL LA should not be administered during nursing. (8.1, 8.3)
- *Pediatric Use:* Efficacy in the pediatric population has not been demonstrated. Safety information from a study of a total of 710 pediatric patients (486 on DETROL LA, 224 on placebo) is available. (8.4)
- *Renal Impairment:* DETROL LA is not recommended for use in patients with CCr <10 mL/min. Dose adjustment in severe renal impairment (CCr: 10-30 mL/min). (8.6)
- *Hepatic Impairment:* Not recommended for use in severe hepatic impairment (Child Pugh Class C). Dose adjustment in mild to moderate hepatic impairment (Child Pugh Class A, B). (8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 08/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

DETROL LA Capsules is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency [*see **CLINICAL STUDIES** (14)*].

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended dose of DETROL LA Capsules is 4 mg once daily with water and swallowed whole. The dose may be lowered to 2 mg daily based on individual response and tolerability; however, limited efficacy data are available for DETROL LA 2 mg [*see **CLINICAL STUDIES** (14)*].

2.2 Dosage Adjustment in Specific Populations

For patients with mild to moderate hepatic impairment (Child-Pugh Class A or B) or severe renal impairment (CCr 10-30 mL/min), the recommended dose of DETROL LA is 2 mg once daily. DETROL LA is not recommended for use in patients with severe hepatic impairment (Child-Pugh Class C). Patients with CCr<10 mL/min have not been studied and use of DETROL LA in this population is not recommended [*see **WARNINGS AND PRECAUTIONS** (5.6) and **USE IN SPECIFIC POPULATIONS** (8.6, 8.7)*].

2.3 Dosage Adjustment in Presence of Concomitant Drugs

For patients who are taking drugs that are potent inhibitors of CYP3A4 [e.g., ketoconazole, clarithromycin, ritonavir], the recommended dose of DETROL LA is 2 mg once daily [*see **DRUG INTERACTIONS** (7.2)*].

3 DOSAGE FORMS AND STRENGTHS

The 2 mg capsules are blue-green with symbol and 2 printed in white ink.

The 4 mg capsules are blue with symbol and 4 printed in white ink.

4 CONTRAINDICATIONS

DETROL LA is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma. DETROL LA is also contraindicated in patients with known hypersensitivity to the drug or its ingredients, or to fesoterodine fumarate extended-release tablets which, like DETROL LA, are metabolized to 5-hydroxymethyl tolterodine [*see **WARNINGS AND PRECAUTIONS** (5.2) (5.3), (5.4)*].

5 WARNINGS AND PRECAUTIONS

5.1 Angioedema

Anaphylaxis and angioedema requiring hospitalization and emergency medical treatment have occurred with the first or subsequent doses of DETROL LA. In the event of difficulty in breathing, upper airway obstruction, or fall in blood pressure, DETROL LA should be discontinued and appropriate therapy promptly provided.

5.2 Urinary Retention

Administer DETROL LA Capsules with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention [*see **CONTRAINDICATIONS** (4)*].

5.3 Gastrointestinal Disorders

Administer DETROL LA with caution in patients with gastrointestinal obstructive disorders because of the risk of gastric retention.

DETROL LA, like other antimuscarinic drugs, may decrease gastrointestinal motility and should be used with caution in patients with conditions associated with decreased gastrointestinal motility (e.g., intestinal atony) [*see **CONTRAINDICATIONS** (4)*].

5.4 Controlled Narrow-Angle Glaucoma

Administer DETROL LA with caution in patients being treated for narrow-angle glaucoma [*see **CONTRAINDICATIONS** (4)*].

5.5 Central Nervous System Effects

Detrol LA is associated with anticholinergic central nervous system (CNS) effects [see Adverse Reactions (6.2)] including dizziness and somnolence [see Adverse Reactions (6.1)]. Patients should be monitored for signs of anticholinergic CNS effects, particularly after beginning treatment or increasing the dose. Advise patients not to drive or operate heavy machinery until the drug's effects have been determined. If a patient experiences anticholinergic CNS effects, dose reduction or drug discontinuation should be considered.

5.6 Hepatic Impairment

The clearance of orally administered tolterodine immediate release was substantially lower in cirrhotic patients than in the healthy volunteers. For patients with mild to moderate hepatic impairment (Child-Pugh Class A or B), the recommended dose for DETROL LA is 2 mg once daily. DETROL LA is not recommended for use in patients with severe hepatic impairment (Child-Pugh Class C) [*see **DOSAGE AND ADMINISTRATION** (2.2) and **USE IN SPECIFIC POPULATIONS** (8.6)*].

5.7 Renal Impairment

Renal impairment can significantly alter the disposition of tolterodine and its metabolites. The dose of DETROL LA should be reduced to 2 mg once daily in patients with severe renal impairment (CCr: 10-30 mL/min). Patients with CCr<10 mL/min have not been studied and use of DETROL LA in this population is not recommended [*see **DOSAGE AND ADMINISTRATION** (2.2) and **USE IN SPECIFIC POPULATIONS** (8.7)*].

5.8 Myasthenia Gravis

Administer DETROL LA with caution in patients with myasthenia gravis, a disease characterized by decreased cholinergic activity at the neuromuscular junction.

5.9 Use in Patients with Congenital or Acquired QT Prolongation

In a study of the effect of tolterodine immediate release tablets on the QT interval [*see* ***CLINICAL PHARMACOLOGY*** *(12.2)*], 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). 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 DETROL LA to patients with a known history of QT prolongation or to patients who are taking Class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications. There has been no association of Torsade de Pointes in the international post-marketing experience with DETROL or DETROL LA.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience

The efficacy and safety of DETROL LA Capsules was evaluated in 1073 patients (537 assigned to DETROL LA; 536 assigned to placebo) who were treated with 2, 4, 6, or 8 mg/day for up to 15 months. These included a total of 1012 patients (505 randomized to DETROL LA 4 mg once daily and 507 randomized to placebo) enrolled in a randomized, placebo-controlled, double-blind, 12-week clinical efficacy and safety study.

Adverse events were reported in 52% (n=263) of patients receiving DETROL LA and in 49% (n=247) of patients receiving placebo. The most common adverse events reported by patients receiving DETROL LA were dry mouth, headache, constipation, and abdominal pain. Dry mouth was the most frequently reported adverse event for patients treated with DETROL LA, occurring in 23.4% of patients treated with DETROL LA and 7.7% of placebo-treated patients. Dry mouth, constipation, abnormal vision (accommodation abnormalities), urinary retention, and dry eyes are expected side effects of antimuscarinic agents. A serious adverse event was reported by 1.4% (n=7) of patients receiving DETROL LA and by 3.6% (n=18) of patients receiving placebo.

Table 1 lists the adverse events, regardless of causality, that were reported in the randomized, double-blind, placebo-controlled 12-week study at an incidence greater than placebo and in greater than or equal to 1% of patients treated with DETROL LA 4 mg once daily.

Table 1. Incidence* (%) of Adverse Events Exceeding Placebo Rate and Reported in ≥1% of Patients Treated with DETROL LA (4 mg daily) in a 12-week, Phase 3 Clinical Trial

Body System	Adverse Event	% DETROL LA n=505	% Placebo n=507
Autonomic Nervous	dry mouth	23	8
General	headache	6	5
	fatigue	2	1
Central/Peripheral Nervous	dizziness	2	1
Gastrointestinal	constipation	6	4
	abdominal pain	4	2
	dyspepsia	3	1
Vision	xerophthalmia	3	2
	vision abnormal	1	0
Psychiatric	somnolence	3	2
	anxiety	1	0
Respiratory	sinusitis	2	1
Urinary	dysuria	1	0

* in nearest integer.

The frequency of discontinuation due to adverse events was highest during the first 4 weeks of treatment. Similar percentages of patients treated with DETROL LA or placebo discontinued treatment due to adverse events. Dry mouth was the most common adverse event leading to treatment discontinuation among patients receiving DETROL LA [n=12 (2.4%) vs. placebo n=6 (1.2%)].

6.2 Post-marketing Experience

The following events have been reported in association with tolterodine use in worldwide post-marketing experience:

General: anaphylaxis and angioedema; *Cardiovascular:* tachycardia, palpitations, peripheral edema; *Gastrointestinal:* diarrhea; *Central/Peripheral Nervous:* confusion, disorientation, memory impairment, hallucinations.

Reports 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.

Because these spontaneously reported events are from the worldwide post-marketing experience, the frequency of events and the role of tolterodine in their causation cannot be reliably determined.

7 DRUG INTERACTIONS

7.1 Potent CYP2D6 Inhibitors

Fluoxetine, a potent inhibitor of CYP2D6 activity, significantly inhibited the metabolism of tolterodine immediate release in CYP2D6 extensive metabolizers, resulting in a 4.8-fold increase in tolterodine AUC. There was a 52% decrease in C_{max} and a 20% decrease in AUC of 5-hydroxymethyl tolterodine (5-HMT), the pharmacologically active metabolite of tolterodine [*see **CLINICAL PHARMACOLOGY** (12.1)*]. The sums of unbound serum concentrations of tolterodine and 5-HMT are only 25% higher during the interaction. No dose

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