Bladder diary

Use this diary to track your bladder habits for a day. Then bring it with you the next time you see your doctor. It may help him or her evaluate if you have overactive bladder (OAB).

date: ___________

<table>
<thead>
<tr>
<th>Time</th>
<th>Drinks/Food What kind? How much?</th>
<th>Trips to Bathroom How many times?</th>
<th>Accidental Leaks How many?</th>
<th>Did you feel a strong urgency to go?</th>
<th>What were you doing at the time?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example</td>
<td>2 cups of coffee</td>
<td>1</td>
<td>0</td>
<td>☑ yes ☐ no</td>
<td>Walking</td>
</tr>
<tr>
<td>Morning</td>
<td></td>
<td></td>
<td></td>
<td>☐ yes ☐ no</td>
<td></td>
</tr>
<tr>
<td>Afternoon</td>
<td></td>
<td></td>
<td></td>
<td>☐ yes ☐ no</td>
<td></td>
</tr>
<tr>
<td>Evening</td>
<td></td>
<td></td>
<td></td>
<td>☐ yes ☐ no</td>
<td></td>
</tr>
<tr>
<td>Overnight</td>
<td></td>
<td></td>
<td></td>
<td>☐ yes ☐ no</td>
<td></td>
</tr>
</tbody>
</table>

Daily total:                  

TOVIAZ® (fesoterodine fumarate) treats the symptoms of overactive bladder (leaks, strong sudden urges to go, going too often).

**Important Safety Information**

If you have certain stomach problems, glaucoma, or cannot empty your bladder, you should not take TOVIAZ.

TOVIAZ may cause allergic reactions that may be serious. If you experience swelling of the face, lips, throat, or tongue, stop taking TOVIAZ and get emergency medical help right away.

Medicines like TOVIAZ can cause blurred vision, dizziness, drowsiness, and decreased sweating. Do not drive, operate machinery, or do unsafe tasks until you know how TOVIAZ affects you. Use caution in hot environments. Drinking alcohol while taking medicines such as TOVIAZ may cause increased drowsiness.

The most common side effects are dry mouth and constipation.

TOVIAZ has benefits and risks. There may be other options. For more information, visit Toviaz.com.

*Please see accompanying Full Prescribing and Patient Information.*
TOVIAZ® (fesoterodine fumarate) extended-release tablets, for oral use

Initial U.S. Approval: 2008

1 INDICATIONS AND USAGE

TOVIAZ is a muscarinic antagonist indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. (1)

2 DOSAGE AND ADMINISTRATION

The recommended starting dose of TOVIAZ is 4 mg once daily. Based upon individual response and tolerability, the dose may be increased to 8 mg once daily. (2)

The daily dose of TOVIAZ should not exceed 4 mg in the following populations:
- Patients with severe renal impairment (ClCR <30 mL/min) (2)
- Patients taking potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, and clarithromycin. (2)

Toviaz is not recommended for use in patients with severe hepatic impairment (Child-Pugh C). (2)

Toviaz should be taken with liquid and swallowed whole. Toviaz can be administered with or without food, and should not be chewed, divided, or crushed. (2)

3 DOSAGE FORMS AND STRENGTHS

Toviaz 4 mg extended-release tablets are light blue, oval, biconvex, film-coated, and engraved with “FS” on one side. (3)

Toviaz 8 mg extended-release tablets are blue, oval, biconvex, film-coated, and engraved with “FT” on one side. (3)

4 CONTRAINDICATIONS

TOVIAZ is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma. Toviaz is also contraindicated in patients with known hypersensitivity to the drug or its ingredients or to tolterodine tartrate or tolterodine tartrate extended-release capsules. (4)

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


5.1 Angioedema
Angioedema of the face, lips, tongue, and/or larynx has been reported with fesoterodine. In some cases angioedema occurred after the first dose. Angioedema associated with upper airway swelling may be life-threatening. If involvement of the tongue, hypopharynx, or larynx occurs, fesoterodine should be promptly discontinued and appropriate therapy and/or measures to ensure a patent airway should be promptly provided.

5.2 Bladder Outlet Obstruction
Toviaz should be administered with caution to patients with clinically significant bladder outlet obstruction because of the risk of urinary retention [see Contraindications (4)].

5.3 Decreased Gastrointestinal Motility
Toviaz, like other antimuscarinic drugs, should be used with caution in patients with decreased gastrointestinal motility, such as those with severe constipation.

5.4 Controlled Narrow-Angle Glaucoma
Toviaz should be used with caution in patients being treated for narrow-angle glaucoma, and only where the potential benefits outweigh the risks [see Contraindications (4)].

5.5 Central Nervous System Effects
Toviaz is associated with anticholinergic central nervous system (CNS) effects [see Adverse Reactions (6.2)]. A variety of CNS anticholinergic effects have been reported, including headache, dizziness, and somnolence. 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 they know how Toviaz affects them. If a patient experiences anticholinergic CNS effects, particularly after beginning treatment or increasing the dose, dose reduction or drug discontinuation should be considered.

5.6 Hepatic Impairment
Toviaz has not been studied in patients with severe hepatic impairment and therefore is not recommended for use in this patient population [see Use in Specific Populations (8.7) and Dosage and Administration (2)].

5.7 Renal Impairment
Doses of Toviaz greater than 4 mg are not recommended in patients with severe renal impairment [see Use in Specific Populations (8.7) and Dosage and Administration (2)].

5.8 Concomitant Administration with CYP3A4 Inhibitors
Doses of Toviaz greater than 4 mg are not recommended in patients taking a potent CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, clarithromycin).

No dosage adjustments are recommended in the presence of moderate CYP3A4 inhibitors (e.g., erythromycin, fluconazole, diltiazem, verapamil and grapefruit juice). While the effect of weak CYP3A4 inhibitors (e.g. cimetidine) was not examined by clinical study, some pharmacokinetic interaction is expected, albeit less than that observed with moderate CYP3A4 inhibitors [see Drug Interactions (7.2) and Dosage and Administration (2)].

5.9 Myasthenia Gravis
Toviaz should be used with caution in patients with myasthenia gravis, a disease characterized by decreased cholinergic activity at the neuromuscular junction.
6.2 Post-marketing Experience
The following events have been reported in association with fesoterodine use in worldwide post-marketing experience: Eye disorders: Blurred vision; Cardiac disorders: Palpitations; General disorders and administrative site conditions: Hypersensitivity reactions, including angioedema with airway obstruction, face edema; Central nervous system disorders: Dizziness, headache, somnolence; Skin and subcutaneous tissue disorders: Urticaria, pruritus.

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

7 DRUG INTERACTIONS
7.1 Antimuscarinic Drugs
Co-administration of Toviaz with other antimuscarinic agents that produce dry mouth, constipation, urinary retention, and other anticholinergic pharmacological effects may increase the frequency and/or severity of such effects. Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility.

7.2 CYP3A4 Inhibitors
Doses of Toviaz greater than 4 mg are not recommended in patients taking potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, and clarithromycin. Co-administration of the potent CYP3A4 inhibitor ketoconazole with fesoterodine led to approximately a doubling of the maximum concentration (C_max) and area under the concentration versus time curve (AUC) of 5-hydroxymethyl tolterodine (5-HMT), the active metabolite of fesoterodine.

Compared with CYP2D6 extensive metabolizers not taking ketoconazole, further increases in the exposure to 5-HMT were observed in subjects who were CYP2D6 poor metabolizers taking ketoconazole (see Clinical Pharmacology (12.3), Warnings and Precautions (5.8), and Dosage and Administration (2)).

There is no clinically relevant effect of moderate CYP3A4 inhibitors on the pharmacokinetics of fesoterodine. Following blockade of CYP3A4 by coadministration of the moderate CYP3A4 inhibitor fluconazole 200 mg twice a day for 2 days, the average (90% confidence interval) increase in C_max and AUC of the active metabolite of fesoterodine was approximately 19% (11% - 28%) and 27% (18% - 36%), respectively. No dosing adjustments are recommended in the presence of moderate CYP3A4 inhibitors (e.g., erythromycin, fluconazole, diltiazem, verapamil and grapefruit juice).

The effect of weak CYP3A4 inhibitors (e.g. cimetidine) was not examined; it is not expected to be in excess of the effect of moderate inhibitors (see Clinical Pharmacology (12.3), Warnings and Precautions (5.8), and Dosage and Administration (2)).

7.3 CYP3A4 Inducers
No dosing adjustments are recommended in the presence of CYP3A4 inducers, such as rifampin and carbamazepine. Following induction of CYP3A4 by coadministration of rifampin 600 mg once a day, C_max and AUC of the active metabolite of fesoterodine decreased by approximately 70% and 75%, respectively, after oral administration of Toviaz 8 mg. The terminal half-life of the active metabolite was not changed.

7.4 CYP2D6 Inhibitors
The interaction with CYP2D6 inhibitors was not tested clinically. In poor metabolizers for CYP2D6, representing a maximum CYP2D6 inhibition, C_max and AUC of the active metabolite are increased 1.7- and 2-fold, respectively.

No dosing adjustments are recommended in the presence of CYP2D6 inhibitors.

7.5 Drugs Metabolized by Cytochrome P450
In vitro data indicate that at therapeutic concentrations, the active metabolite of fesoterodine does not have the potential to inhibit or induce Cytochrome P450 enzyme systems (see Clinical Pharmacology (12.3)).

7.6 Oral Contraceptives
In the presence of fesoterodine, there are no clinically significant changes in the plasma concentrations of combined oral contraceptives containing ethinyl estradiol and levonorgestrel (see Clinical Pharmacology (12.3)).

7.7 Warfarin
A clinical study has shown that fesoterodine 8 mg once daily has no significant effect on the pharmacokinetics or the anticoagulant activity (PT/INR) of warfarin 25 mg. Standard therapeutic monitoring for warfarin should be continued (see Clinical Pharmacology (12.3)).

7.8 Drug-Laboratory Test Interactions
Interactions between Toviaz and laboratory tests have not been studied.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary
There are no data with the use of Toviaz in pregnant women to inform a drug associated risk for birth defects or miscarriage. In animal reproduction studies, oral administration of fesoterodine to pregnant mice and rabbits during organogenesis resulted in fetotoxicity at maternal exposures that were 6 and 3 times respectively the maximum recommended human dose (MRHD) of 8 mg/day, based on AUC (see Data). The background risk of major birth defects and miscarriage for the indicated population is unknown. However, in the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data
No dose-related teratogenicity was observed in reproduction studies performed in mice and rabbits. In mice at 6 to 27 times the expected exposure at the maximum recommended human dose (MRHD) of 8 mg based on AUC (75 mg/kg/day, oral), increased resorptions and decreased live fetuses were observed. One fetus with cleft palate was observed at each dose (15, 45, and 75 mg/kg/day), at an incidence within the background historical range.

In rabbits treated at 3 to 11 times the MRHD (27 mg/kg/day, oral), incompletely ossified sternebrae (retardation of bone development) and reduced survival were observed in fetuses. In rabbits at 9 to 11 times the MRHD (4.5 mg/kg/day, subcutaneous), maternal toxicity and incompletely ossified sternebrae were observed in fetuses (at an incidence within the background historical range). In rabbits at 3 times the MRHD (1.5 mg/kg/day, subcutaneous), decreased maternal food consumption in the absence of any fetal effects was observed. Oral administration of 30 mg/kg/day fesoterodine to mice in a pre- and post-natal development study resulted in decreased body weight of the dams and delayed ear opening of the pups. No effects were noted on mating and reproduction of the F1 dams or on the F2 offspring.

8.2 Lactation
Risk Summary
There is no information on the presence of fesoterodine in human milk, the effects on the breastfed child, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for Toviaz and any potential adverse effects on the breastfed child from Toviaz or from the underlying maternal condition.

8.4 Pediatric Use
The pharmacokinetics of fesoterodine have not been evaluated in pediatric patients. The safety and effectiveness of Toviaz in pediatric patients have not been established.

8.5 Geriatric Use
No dose adjustment is recommended for the elderly. The pharmacokinetics of fesoterodine are not significantly influenced by age.

Of 1567 patients who received Toviaz 4 mg/day or 8 mg/day in the Phase 2 and 3, placebo-controlled, efficacy and safety studies, 315 (33%) were 65 years of age or older, and 140 (9%) were 75 years of age or older. No overall differences in safety or effectiveness were observed between patients younger than 65 years of age and those 65 years of age or older in these studies; however, the incidence of antimuscarinic adverse events, including dry mouth, constipation, dyspepsia, increase in residual urine, dizziness (at 8 mg only) and urinary tract infection, was higher in patients 75 years of age and older as compared to younger patients (see Clinical Studies (14) and Adverse Reactions (6)).

8.6 Renal Impairment
In patients with severe renal impairment (C_LCR <30 mL/min), C_max and AUC are increased 2.0- and 2.3-fold, respectively. Doses of Toviaz greater than 4 mg are not recommended in patients with severe renal impairment. In patients with mild or moderate renal impairment (C_LCR ranging from 30-80 mL/min), C_max and AUC of the active metabolite are increased up to 1.5- and 1.8-fold, respectively, as compared to healthy subjects. No dose adjustment is recommended in patients with mild or moderate renal impairment (see Warnings and Precautions (5.7) and Dosage and Administration (2)).

8.7 Hepatic Impairment
Patients with severe hepatic impairment (Child-Pugh C) have not been studied; therefore Toviaz is not recommended for use in these patients. In patients with moderate (Child-Pugh B) hepatic impairment, C_max and AUC of the active metabolite are increased 1.4- and 2.1-fold, respectively, as compared to healthy subjects. No dose adjustment is recommended in patients with mild or moderate hepatic impairment (see Warnings and Precautions (5.8) and Dosage and Administration (2)).

8.8 Gender
No dose adjustment is recommended based on gender. The pharmacokinetics of fesoterodine are not significantly influenced by gender.

8.9 Race
Available data indicate that there are no differences in the pharmacokinetics of fesoterodine between Caucasian and Black healthy subjects following administration of Toviaz.

10 OVERDOSAGE
Overdosage with Toviaz can result in severe anticholinergic effects. Treatment should be symptomatic and supportive. In the event of overdosage, ECG monitoring is recommended.

11 DESCRIPTION
Toviaz contains fesoterodine fumarate and is an extended-release tablet. Fesoterodine is rapidly de-esterified to its active metabolite (R)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol, or 5-hydroxymethyl tolterodine, which is a muscarinic receptor antagonist.
Chemically, fesoterodine fumarate is designated as isotamibucic acid 2-(R)-3-diisopropylammonium-1-phenylpropyl)-4-(hydroxymethyl) phenyl ester hydrogen fumarate. The empirical formula is C30H41NO7 and its molecular weight is 527.66. The structural formula is:

The asterisk (*) indicates the chiral carbon.

Fesoterodine fumarate is a white to off-white powder, which is freely soluble in water. Each Toviaz extended-release tablet contains either 4 mg or 8 mg of fesoterodine fumarate and the following inactive ingredients: glyceryl beheenate, hypromellose, indig carmine aluminum lake, lactose monohydrate, soya lecithin, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and xylitol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Fesoterodine is a competitive muscarinic receptor antagonist. After oral administration, fesoterodine is rapidly and extensively hydrolyzed by nonspecific esterases to its active metabolite, 5-hydroxymethyl tolterodine, which is responsible for the antimuscarinic activity of fesoterodine and is also one of the active moieties of tolterodine tartrate tablets and tolterodine tartrate extended-release capsules.

Muscarinic receptors play a role in contractions of urinary bladder smooth muscle and stimulation of salivary secretion. Inhibition of these receptors in the bladder is presumed to be the mechanism by which fesoterodine produces its effects.

12.2 Pharmacodynamics
In a urodynamics study involving patients with involuntary detrusor contractions, the effects after the administration of fesoterodine on the volume at first detrusor contraction and bladder capacity were assessed. Administration of fesoterodine increased the volume at first detrusor contraction and bladder capacity in a dose-dependent manner. These findings are consistent with an antimuscarinic effect on the bladder.

Cardiac Electrophysiology: The effect of fesoterodine 4 mg and 28 mg on the QT interval was evaluated in a double-blind, randomized, placebo- and positive-controlled (moxifloxacin 400 mg once a day) parallel trial with once-daily treatment over a period of 3 days in 261 male and female subjects aged 44 to 65 years. Electrocardiographic parameters were measured over a 24-hour period at pre-dose, after the first administration, and after the third administration of study medication. Fesoterodine 28 mg was chosen because this dose, when administered to CYP2D6 extensive metabolizers, results in an exposure to the active metabolite that is similar to the exposure in a CYP2D6 poor metabolizer receiving fesoterodine 8 mg together with CYP3A4 blockade. Corrected QT intervals (QTc) were calculated using Fridericia's correction and a linear individual correction method. Analyses of 24-hour average QTc, time-matched baseline-corrected QTc, and time-matched placebo- subtracted QTc intervals indicate that fesoterodine at doses of 4 and 28 mg/day did not prolong the QT interval. The sensitivity of the study was shown by positive QTc prolongation using moxifloxacin.

Toviaz is associated with an increase in heart rate that correlates with increasing dose. In the study described above, when compared to placebo, the mean increase in heart rate associated with a dose of 4 mg/day and 28 mg/day of fesoterodine was 3 beats/minute and 11 beats/minute, respectively.

In the two, phase 3, placebo-controlled studies in patients with overactive bladder, the mean increase in heart rate compared to placebo was approximately 3-4 beats/minute in the 4 mg/day group and 3-5 beats/minute in the 8 mg/day group.

12.3 Pharmacokinetics

Absorption: After oral administration, fesoterodine is well absorbed. Due to rapid and extensive hydrolysis by nonspecific esterases to its active metabolite 5-hydroxymethyl tolterodine, fesoterodine cannot be detected in plasma. Bioavailability of the active metabolite is 52%. After single or multiple-dose oral administration of fesoterodine in doses from 4 mg to 28 mg, plasma concentrations of the active metabolite are proportional to the dose. Maximum plasma levels are reached after approximately 5 hours. No accumulation occurs after multiple-dose administration.

A summary of pharmacokinetic parameters for the active metabolite after a single dose of Toviaz 4 mg and 8 mg in extensive and poor metabolizers of CYP2D6 is provided in Table 2.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Toviaz 4 mg</th>
<th>Toviaz 8 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>1.89 [43%]</td>
<td>3.45 [54%]</td>
</tr>
<tr>
<td>AUC0-t (ng*h/mL)</td>
<td>21.2 [38%]</td>
<td>40.5 [31%]</td>
</tr>
<tr>
<td>tmax (h)</td>
<td>5 [5-6]</td>
<td>5 [5-6]</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>7.31 [27%]</td>
<td>7.31 [30%]</td>
</tr>
</tbody>
</table>

EM = extensive CYP2D6 metabolizer, PM = poor CYP2D6 metabolizer, CV = coefficient of variation; Cmax = maximum plasma concentration, AUC0-tz = area under the concentration time curve from zero up to the last measurable plasma concentration, tmax = time to reach Cmax, t1/2 = terminal half-life.

Effect of Food: There is no clinically relevant effect of food on the pharmacokinetics of fesoterodine. In a study of the effects of food on the pharmacokinetics of fesoterodine in 16 healthy male volunteers, concomitant food intake increased the active metabolite of fesoterodine AUC by approximately 19% and Cmax by 18% [see Dosage and Administration (2)].

Distribution: Plasma protein binding of the active metabolite is low (approximately 50%) and is primarily bound to albumin and alpha-1-acid glycoprotein. The mean steady-state volume of distribution following intravenous infusion of the active metabolite is 169 L.

Metabolism: After oral administration, fesoterodine is rapidly and extensively hydrolyzed to its active metabolite. The active metabolite is further metabolized in the liver to its carboxy, carboxy-N-desisopropyl, and N-desisopropyl metabolites via two major pathways involving CYP2D6 and CYP3A4. None of these metabolites contribute significantly to the antimuscarinic activity of fesoterodine.

Variability in CYP2D6 Metabolism: A subset of individuals (approximately 7% of Caucasians and approximately 2% of African Americans) are poor metabolizers for CYP2D6. Cmax and AUC of the active metabolite are increased 1.7- and 2-fold, respectively, in CYP2D6 poor metabolizers, as compared to extensive metabolizers.

Excretion: Hepatic metabolism and renal excretion contribute significantly to the elimination of the active metabolite. After oral administration of fesoterodine, approximately 70% of the administered dose was recovered in urine as the active metabolite (16%), carboxy metabolite (34%), carboxy-N-desisopropyl metabolite (18%), or N-desisopropyl metabolite (1%), and a smaller amount (7%) was recovered in feces.

The terminal half-life of the active metabolite is approximately 4 hours following an intravenous administration. The apparent terminal half-life following oral administration is approximately 7 hours.

Pharmacokinetics in Specific Populations

Geriatric Patients: Following a single 8 mg oral dose of fesoterodine, the mean (±SD) AUC and Cmax for the active metabolite 5-hydroxymethyl tolterodine in 12 elderly men (mean age 67 years) were 51.8 ± 26.1 ng*h/mL and 3.8 ± 1.7 ng/mL, respectively. In the same study, the mean (±SD) AUC and Cmax in 12 young men (mean age 30 years) were 52.0 ± 31.5 ng*h/mL and 4.1 ± 2.1 ng/mL, respectively. The pharmacokinetics of fesoterodine were not significantly influenced by age [see Use in Specific Populations (8.5)].

Pediatric Patients: The pharmacokinetics of fesoterodine have not been evaluated in pediatric patients [see Use in Specific Populations (8.4)].

Gender: Following a single 8 mg oral dose of fesoterodine, the mean (±SD) AUC and Cmax for the active metabolite 5-hydroxymethyl tolterodine in 12 elderly men (mean age 67 years) were 51.8 ± 26.1 ng*h/mL and 3.8 ± 1.7 ng/mL, respectively. In the same study, the mean (±SD) AUC and Cmax in 12 elderly women (mean age 68 years) were 56.0 ± 28.8 ng*h/mL and 4.6 ± 2.3 ng/mL, respectively. The pharmacokinetics of fesoterodine were not significantly influenced by gender [see Use in Specific Populations (8.8)].

Race: The effects of Caucasian or Black race on the pharmacokinetics of fesoterodine were examined in a study of 12 Caucasian and 12 Black African young male volunteers. Each subject received a single oral dose of 8 mg fesoterodine. The mean (±SD) AUC and Cmax in Black males were 65.8 ± 23.2 ng*h/mL and 5.5 ± 1.9 ng/mL, respectively. The pharmacokinetics of fesoterodine were not significantly influenced by race [see Use in Specific Populations (8.9)].

Renal Impairment: In patients with mild or moderate renal impairment (Clcr ranging from 30-80 mL/min), Cmax and AUC of the active metabolite are increased up to 1.5- and 1.8-fold, respectively, as compared to healthy subjects. In patients with severe renal impairment (Clcr <30 mL/min), Cmax and AUC are increased 2.0- and 2.3-fold, respectively [see Use in Specific Populations (8.6), Warnings and Precautions (5.7), and Dosage and Administration (2)].

Hepatic Impairment: In patients with moderate (Child-Pugh B) hepatic impairment, Cmax and AUC of the active metabolite are increased 1.4- and 2.1-fold, respectively, as compared to healthy subjects. Subjects with severe hepatic impairment (Child-Pugh C) have not been studied [see Use in Specific Populations (8.7), Warnings and Precautions (5.6), and Dosage and Administration (2)].
14 CLINICAL STUDIES

Toviaz extended-release tablets were evaluated in two, Phase 3, randomized, double-blind, placebo-controlled, 12-week studies for the treatment of overactive bladder with symptoms of urinary incontinence, urgency, and urinary frequency. Entry criteria required that patients have symptoms of overactive bladder for ≥6-months duration, at least 8 micturitions per day, and at least 6 urinary urgency episodes or ≥3 urge incontinence episodes per 3-day diary period. Patients were randomized to a fixed dose of Toviaz 4 mg/day or placebo. In one of these studies, 290 patients were randomized to an active control arm (an oral antimuscarinic agent). For the combined studies, a total of 554 patients received placebo, 554 patients received Toviaz 4 mg/day, and 566 patients received Toviaz 8 mg/day. The majority of patients were Caucasian (91%) and female (79%) with a mean age of 58 years (range 19-91 years).

The primary efficacy endpoints were the mean change in the number of urge urinary incontinence episodes per 24 hours and the mean change in the number of micturitions (frequency) per 24 hours. An important secondary endpoint was the mean change in the voided volume per micturition.

Results for the primary endpoints and for mean change in voided volume per micturition from the two 12-week clinical studies of Toviaz are reported in Table 3.

### Table 3: Mean baseline and change from baseline to Week 12 for urge urinary incontinence episodes, number of micturitions, and volume voided per micturition

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo N=279</td>
<td>Toviaz 4mg/day N=265</td>
</tr>
<tr>
<td>Number of urge incontinence episodes per 24 hours*</td>
<td>3.7</td>
<td>3.8</td>
</tr>
<tr>
<td>p-value vs. placebo</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-1.20</td>
<td>-2.06</td>
</tr>
<tr>
<td>Number of micturitions per 24 hours</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>p-value vs. placebo</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>10</td>
<td>27</td>
</tr>
<tr>
<td>Voided volume per micturition (mL)</td>
<td>3.7</td>
<td>3.8</td>
</tr>
<tr>
<td>p-value vs. placebo</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Only those patients who were urge incontinent at baseline were included for the analysis of number of urge urinary incontinence episodes per 24 hours: In Study 1, the number of these patients was 211, 199, and 223 in the placebo, Toviaz 4 mg/day and Toviaz 8 mg/day groups, respectively. In Study 2, the number of these patients was 205, 228, and 218, respectively.

Figures 1-4: The following figures show change from baseline over time in number of micturitions and urge urinary incontinence episodes per 24 h in the two studies.

**Figure 1:** Change in Number of Micturitions per 24 h (Study 1)

**Figure 2:** Change in Urge Incontinence Episodes per 24 h (Study 1)

### 13 NONCLINICAL TOXICOLOGY

#### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of drug-related carcinogenicity was found in 24-month studies with oral administration to mice and rats. The highest tolerated doses in mice (females 45 to 60 mg/kg/day, males 30 to 45 mg/kg/day) correspond to 11 to 19 times (females) and 4 to 9 times (males) the estimated human AUC values reached with fesoterodine 8 mg, which is the Maximum Recommended Human Dose (MRHD). In rats, the highest tolerated dose (45 to 60 mg/kg/day) corresponds to 3 to 8 times (females) and 3 to 14 times (males) the estimated human AUC at the MRHD.

Fesoterodine was not mutagenic or genotoxic *in vitro* (Ames tests, chromosome aberration tests) or *in vivo* (mouse micronucleus test).

Fesoterodine had no effect on male reproductive function or fertility at doses up to 45 mg/kg/day in mice. At 45 mg/kg/day, a lower number of corpora lutea, implantation sites and viable fetuses was observed in female mice administered fesoterodine for 2 weeks prior to mating and through day 7 of gestation. The maternal No-Observed-Effect Level (NOEL) and the NOEL for effects on reproduction and early embryonic development were both 15 mg/kg/day. At the NOEL, the systemic exposure, based on AUC, was 0.6 to 1.5 times higher in mice than in humans at the MRHD, whereas based on peak plasma concentrations, the exposure in mice was 5 to 9 times higher.
A reduction in number of urge urinary incontinence episodes per 24 hours was observed for both doses as compared to placebo as early as two weeks after starting Toviaz therapy.
Read the Patient Information that comes with TOVIAZ before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or your treatment.

What is TOVIAZ?
TOVIAZ is a prescription medicine used in adults to treat symptoms of a condition called overactive bladder, including:
- Urge urinary incontinence -- leaking or wetting accidents due to a strong need to urinate,
- Urinary urgency -- having a strong need to urinate right away,
- Urinary frequency -- having to urinate too often.

TOVIAZ has not been studied in children.

Who should not take TOVIAZ?
Do not take TOVIAZ if you:
- Are not able to empty your bladder (urinary retention)
- Have delayed or slow emptying of your stomach (gastric retention)
- Have an eye problem called “uncontrolled narrow-angle glaucoma”
- Are allergic to TOVIAZ or any of its ingredients. See the end of this leaflet for a complete list of ingredients
- Are allergic to Detrol® or Detrol® LA, which contains tolerodine.

What should I tell my doctor before starting TOVIAZ?
Before starting TOVIAZ, tell your doctor about all of your medical and other conditions that may affect the use of TOVIAZ, including:
- Stomach or intestinal problems or problems with constipation
- Problems emptying your bladder or if you have a weak urine stream
- Treatment for an eye problem called narrow-angle glaucoma
- Kidney problems
- Liver problems
- A condition called myasthenia gravis
- If you are pregnant or trying to become pregnant. It is not known if TOVIAZ can harm your unborn baby.
- If you are breastfeeding. It is not known if TOVIAZ passes into breast milk or if it can harm your baby. Talk to your doctor about the best way to feed your baby if you take TOVIAZ.

Before starting TOVIAZ, tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal products. TOVIAZ may affect the way other medicines work, and other medicines may affect how TOVIAZ works. Especially tell your doctor if you are taking antibiotics or antifungal medicines.

Know all the medicines you take. Keep a list of them with you to show your doctor and pharmacist each time you get a new medicine.

How should I take TOVIAZ?
- Take TOVIAZ exactly as your doctor tells you to take it.
- Your doctor may give you the lower 4 mg dose of TOVIAZ if you have certain medical conditions, such as severe kidney problems.
- Take TOVIAZ with liquid and swallow the tablet whole. Do not chew, divide, or crush the tablet.
- You can take TOVIAZ with or without food.
- If you miss a dose of TOVIAZ, begin taking TOVIAZ again the next day. Do not take 2 doses of TOVIAZ in the same day. If you take too much TOVIAZ, call your doctor or go to an emergency department right away.

What are the possible side effects of TOVIAZ?
TOVIAZ may cause allergic reactions that may be serious. Symptoms of a serious allergic reaction may include swelling of the face, lips, throat or tongue. If you experience these symptoms, you should stop taking TOVIAZ and get emergency medical help right away.

The most common side effects of TOVIAZ are:
- Dry mouth
- Constipation

TOVIAZ may cause other less common side effects, including:
- Dry eyes
- Trouble emptying the bladder

Tell your doctor if you have any side effects that bother you or that do not go away.

Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088. These are not all of the possible side effects of TOVIAZ. For a complete list, ask your doctor.

How should I store TOVIAZ?
- Store TOVIAZ at room temperature, 68° to 77°F (20° to 25°C); brief periods permitted between 59° to 86°F (15° to 30°C)
- Protect the medicine from moisture by keeping the bottle closed tightly.
- Safely throw away TOVIAZ that is out of date or no longer needed.

Keep TOVIAZ and all medicines out of the reach of children.

General information about TOVIAZ
Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Only use TOVIAZ the way your doctor tells you. Do not give TOVIAZ to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about TOVIAZ. If you would like more information, talk with your doctor. You can ask your doctor for information about TOVIAZ that is written for healthcare professionals. You can also call 1-877-9-TOVIAZ (1-877-986-8429) or go to www.TOVIAZ.com.

What are the ingredients in TOVIAZ?
Active ingredient: fesoterodine fumarate
Inactive ingredients: glyceryl behenate, hypromellose, indigo carmine aluminum lake, lactose monohydrate, soya lecithin, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and xylitol.

This product’s label may have been updated. For current full prescribing information, please visit www.pfizer.com.