TOVIAZ™

(fesoterodine fumarate)

extended-release tablets

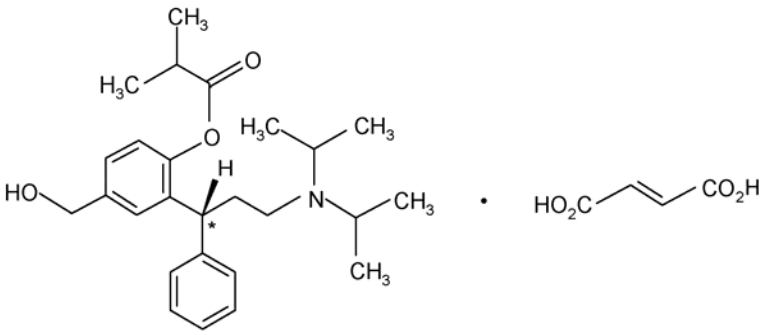
Rx only

Prescribing Information

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 isobutyric acid 2-((R)-3-diisopropylammonium-1-phenylpropyl)-4-(hydroxymethyl)phenyl ester hydrogen fumarate. The empirical formula is $C_{30}H_{41}NO_7$ 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 behenate, hypromellose, indigo carmine aluminum lake, lactose monohydrate, soya lecithin, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and xylitol.

CLINICAL PHARMACOLOGY

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.

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.

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Pharmacodynamics

In a urodynamic 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.

Pharmacokinetics

Absorption

After oral administration, fesoterodine is well absorbed. Due to rapid and extensive hydrolysis by nonspecific esterases to its active metabolite, 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 1.

Table 1 Summary of geometric mean [CV] pharmacokinetic parameters for the active metabolite after a single dose of Toviaz 4 mg and 8 mg in extensive and poor CYP2D6 metabolizers

	Toviaz 4 mg		**Toviaz 8 mg**	
Parameter	**EM (n=16)**	**PM (n=8)**	**EM (n=16)**	**PM (n=8)**
C_{max} (ng/mL)	1.89 [43%]	3.45 [54%]	3.98 [28%]	6.90 [39%]
$AUC_{0\text{-}tz}$ (ng*h/mL)	21.2 [38%]	40.5 [31%]	45.3 [32%]	88.7 [36%]
t_{max} (h)[a]	5 [2-6]	5 [5-6]	5 [3-6]	5 [5-6]
$t_{½}$ (h)	7.31 [27%]	7.31 [30%]	8.59 [41%]	7.66 [21%]

EM = extensive CYP2D6 metabolizer, PM = poor CYP2D6 metabolizer, CV=coefficient of variation

C_{max} = maximum plasma concentration, $AUC_{0\text{-}tz}$ = area under the concentration time curve from zero up to the last measurable plasma concentration, t_{max} = time to reach C_{max}, $t_{½}$= terminal half-life

[a] Data presented as median (range)

Effect of Food

There is no clinically relevant effect of food on the pharmacokinetics of fesoterodine. (see DOSAGE AND ADMINISTRATION)

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.

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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 Metabolism: A subset of individuals (approximately 7% Caucasians and 2% African Americans) are poor metabolizers for CYP2D6. The remainder of the population is referred to as extensive metabolizers. C_{max} 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 Special Populations

Age

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

Pediatric

The pharmacokinetics of fesoterodine have not been evaluated in pediatric patients.

Gender

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

Race

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

Renal Insufficiency

In patients with mild or moderate renal insufficiency (CL_{CR} 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. In patients with severe renal insufficiency (CL_{CR} < 30 mL/min), C_{max} and AUC are increased 2.0- and 2.3-fold, respectively.

In patients with mild or moderate renal insufficiency, no dose adjustment is recommended. Doses of Toviaz greater than 4 mg are not recommended in patients with severe renal insufficiency (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

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Hepatic Impairment

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. Subjects with severe hepatic impairment (Child-Pugh C) have not been studied; therefore Toviaz is not recommended for use in these patients (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Drug-Drug Interactions

Drugs Metabolized by Cytochrome P450

At therapeutic concentrations, the active metabolite of fesoterodine does not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4, or induce CYP1A2, 2B6, 2C9, 2C19, or 3A4 in vitro.

CYP3A4 Inhibitors

Following blockade of CYP3A4 by coadministration of the potent CYP3A4 inhibitor ketoconazole 200 mg twice a day for 5 days, C_{max} and AUC of the active metabolite of fesoterodine increased 2.0- and 2.3-fold, respectively, after oral administration of Toviaz 8 mg to CYP2D6 extensive metabolizers. In CYP2D6 poor metabolizers, C_{max} and AUC of the active metabolite of fesoterodine increased 2.1- and 2.5-fold, respectively, during co-administration of ketoconazole 200 mg twice a day for 5 days. C_{max} and AUC were 4.5- and 5.7-fold higher, respectively, in subjects who were CYP2D6 poor metabolizers and taking ketoconazole compared to subjects who were CYP2D6 extensive metabolizers and not taking ketoconazole. In a separate study coadministering fesoterodine with ketoconazole 200 mg once a day for 5 days, the C_{max} and AUC values of the active metabolite of fesoterodine were increased 2.2-fold in CYP2D6 extensive metabolizers and 1.5- and 1.9-fold, respectively, in CYP2D6 poor metabolizers. C_{max} and AUC were 3.4- and 4.2-fold higher, respectively, in subjects who were CYP2D6 poor metabolizers and taking ketoconazole compared to subjects who were CYP2D6 extensive metabolizers and not taking ketoconazole.

Therefore, doses of Toviaz greater than 4mg are not recommended in patients taking potent CYP3A4 inhibitors, such as ketoconazole, itraconazole and clarithromycin (see PRECAUTIONS, Drug Interactions and DOSAGE and ADMINISTRATION).

The effects of weak or moderate CYP3A4 inhibitors were not examined.

CYP3A4 Inducers

Following induction of CYP3A4 by coadministration of rifampicin 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.

Induction of CYP3A4 may lead to reduced plasma levels. No dosing adjustments are recommended in the presence of CYP3A4 inducers.

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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.

Oral Contraceptives

In the presence of fesoterodine, there are no changes in the plasma concentrations of combined oral contraceptives containing ethinyl estradiol and levonorgestrel.

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 confirmed by positive QTc prolongation by 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.

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 urge 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 or 8 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

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