PRODUCT MONOGRAPH

PrAPO-FESOTERODINE

Fesoterodine Fumarate Extended-Release Tablets

4 mg and 8 mg

Anticholinergic - Antispasmodic Agent

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Fesoterodine Fumarate Extended-Release Tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
oral	Extended-release tablets 4 mg, 8 mg	Colloidal silicon dioxide, glyceryl behenate, hypromellose, indigotine AL lake, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

INDICATIONS AND CLINICAL USE

APO-FESOTERODINE (fesoterodine fumarate extended-release tablet) is indicated for the treatment of patients with overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence, or any combination of these symptoms.

Geriatrics (> 65 years of age):
Based on clinical studies, no apparent overall differences were observed in safety between older (patients ≥ 65 years) and younger patients (patients < 65 years) on fesoterodine extended-release tablets. Therefore, dosage adjustment for geriatric patients may not be required (see **WARNINGS AND PRECAUTIONS**, **Special Populations**).

Pediatrics (< 18 years of age):
The safety and efficacy of fesoterodine fumarate in pediatric populations have not been established.

CONTRAINDICATIONS

- Urinary retention
- Gastric retention
- Uncontrolled narrow-angle glaucoma
- Hypersensitivity to this drug, tolterodine L-tartrate tablets, tolterodine L-tartrate extended-release capsules, any of the ingredients in the formulation or any component of the container. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING**.

WARNINGS AND PRECAUTIONS

Cardiovascular

Fesoterodine fumarate, like other antimuscarinic drugs, is associated with increased heart rate that correlates with increasing dose (see **ACTION AND CLINICAL PHARMACOLOGY,** ***Cardiac Electrophysiology and Hemodynamics***). Although there are no clinical trial or post-marketing data to confirm the potential for fesoterodine fumarate to aggravate certain pre-existing cardiac conditions, this product is in the class anticholinergic medications which are known to have cardiac effects. Prescribers should therefore use caution when prescribing APO-FESOTERODINE to patients with ischemic heart disease, congestive heart failure, cardiac arrhythmias, or tachycardia.

Endocrine/Metabolism

CYP3A4

Caution should be exercised when prescribing or up-titrating fesoterodine from 4 mg to 8 mg in patients in whom an increased exposure to the active metabolite is expected, such as with concomitant administration of CYP3A4 inhibitors.

In the presence of a potent CYP3A4 inhibitor (e.g. ketoconazole, itraconazole, miconazole and clarithromycin), doses of APO-FESOTERODINE greater than 4 mg are not recommended.

In the presence of moderate CYP3A4 inhibitors (e.g. fluconazole), no dosing adjustments are recommended.

While the effect of weak CYP3A4 inhibitors (e.g. cimetidine) was not examined in a clinical study, some pharmacokinetic interaction is expected, though less than what was observed with moderate CYP3A4 inhibitors (see **DRUG INTERACTIONS - Drug-drug Interactions, DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY- Pharmacokinetics, Metabolism**).

CYP2D6

A subset of individuals are poor metabolizers for CYP2D6 (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Metabolism**, variability in CYP2D6 Metabolism).

Compared with CYP2D6 extensive metabolizers not taking ketoconazole (a potent CYP3A4 inhibitor), further increases in the exposure to the active metabolite of fesoterodine were observed in subjects who were CYP2D6 poor metabolizers taking ketoconazole (see **DRUG INTERACTIONS, Drug-Drug interactions**, Table 2).

Gastrointestinal

Patients at Risk of Gastric Retention

APO-FESOTERODINE (fesoterodine fumarate extended-release tablets), like other antimuscarinic drugs, should be administered with caution to patients with decreased gastrointestinal motility, including patients with severe constipation and to patients with gastrointestinal obstruction disorders (e.g. pyloric stenosis) because of the risk of gastric retention (see **CONTRAINDICATIONS**).

Genitourinary

Patients at Risk of Urinary Retention

APO-FESOTERODINE, like other antimuscarinic drugs, should be administered with caution to patients with clinically significant bladder outlet obstruction because of the risk of urinary retention (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS, Use With Other Concomitant Therapies,** *Alpha-blockers for lower urinary tract symptoms (LUTS) in men*).

Hepatic/Biliary/Pancreatic

APO-FESOTERODINE should be administered with caution to patients with impaired hepatic function. In patients with mild to moderate hepatic impairment, no dosage adjustment is required.

Fesoterodine is not recommended for use in patients with severe hepatic impairment (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY- Special Populations and Conditions**).

Immune

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.

Neurologic

APO-FESOTERODINE, like other antimuscarinic drugs, should be administered with caution to patients with myasthenia gravis.

Ophthalmologic

Controlled Narrow-Angle Glaucoma

APO-FESOTERODINE, like other antimuscarinic drugs, should be used with caution in patients being treated for narrow-angle glaucoma **(**see **CONTRAINDICATIONS)**.

Renal

APO-FESOTERODINE should be administered with caution to patients with impaired renal function. In patients with mild to moderate renal impairment, no dosage adjustment is required. Doses of fesoterodine greater than 4 mg are not recommended in patients with severe renal impairment (CL_{CR} <30 mL/min) (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY- Special Populations and Conditions).**

Special Populations

Fertility: No clinical trials have been conducted to assess the effect of fesoterodine on human fertility. Findings in mice at maternally toxic doses at exposures approximately 5 to 19 times (based on lowest and highest total systemic exposure) those at the Maximum Recommended Human Dose (MRHD) show an effect on female fertility, however, the clinical implications of these animal findings are not known (see **TOXICOLOGY, Reproduction and Teratology**).

Pregnant Women: There are no adequate data from the use of fesoterodine in pregnant women. The potential risk for humans is unknown. Therefore, fesoterodine should be used during pregnancy only if the potential benefit to the mother outweighs the potential risk to the foetus. Women of childbearing potential should be considered for treatment only if using adequate contraception. In animal reproduction studies, oral administration of fesoterodine to pregnant mice and rabbits during organogenesis resulted in fetotoxicity at maternal exposures that were 7 and 6 times the MRHD, respectively, based on the lowest unbound systemic exposure (see **TOXICOLOGY, Reproduction and Teratology**).

Nursing Women: It is not known whether fesoterodine is excreted into human milk; therefore, breastfeeding is not recommended during treatment with fesoterodine.

Pediatrics (< 18 years of age): The safety and efficacy of fesoterodine fumarate in pediatric patients have not been established.

Geriatrics (> 65 years of age): 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 the clinical studies. However, patients in these studies were highly selected and relatively healthy. The pharmacokinetics of fesoterodine are not significantly influenced by age. Dose adjustment may not be required for the elderly (see **ADVERSE REACTIONS – Geriatrics; DETAILED PHARMACOLOGY – Pharmacokinetic Special population)**.

Information For Patients

Patients should be advised not to engage in potentially hazardous activities, such as driving a car or operating dangerous machines, until they know how APO-FESOTERODINE may affect them (see **ADVERSE REACTIONS**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Due to the pharmacological properties of fesoterodine, treatment may cause mild to moderate antimuscarinic effects like dry mouth, constipation, dry eyes, and dyspepsia.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

The safety of fesoterodine fumarate extended-release tablet was primarily evaluated in Phase 2 and 3 controlled trials in a total of 2859 patients with overactive bladder of which 2288 were treated with fesoterodine. Of this total, 782 received fesoterodine fumarate 4 mg/day, and 785 received fesoterodine fumarate 8 mg/day in Phase 2 or 3 studies with treatment periods of 8 or 12 weeks.

Approximately 80% of these patients had >10 weeks exposure to fesoterodine fumarate.

A total of 1964 patients participated in two 12-week, Phase 3 efficacy and safety studies and subsequent open-label extension studies. In these 2 studies combined, 554 patients received fesoterodine fumarate 4 mg/day and 566 patients received fesoterodine fumarate 8 mg/day.

In Phase 2 and 3 placebo-controlled trials combined, the incidences of serious adverse events in patients receiving placebo, fesoterodine fumarate 4 mg, and fesoterodine fumarate 8 mg were 1.9%, 3.5%, and 2.9%, respectively. All serious adverse events were judged to be not related or unlikely to be related to study medication by the investigator, except for four patients receiving fesoterodine fumarate who reported one serious adverse event each: angina, chest pain, gastroenteritis, and QT prolongation on ECG.

The most commonly reported adverse event in patients treated with fesoterodine fumarate was dry mouth. The incidence of dry mouth was higher in those taking 8 mg/day (35%) and in those taking 4 mg/day (19%), as compared to placebo (7%). Dry mouth led to discontinuation in 0.4%, 0.4%, and 0.8% of patients receiving placebo, fesoterodine fumarate 4 mg, and fesoterodine fumarate 8 mg, respectively. For those patients who reported dry mouth, most had their first occurrence of the event within the first month of treatment.

The second most commonly reported adverse event was constipation. The incidence of constipation was 2% in those taking placebo, 4% in those taking fesoterodine fumarate 4 mg/day, and 6% in those taking fesoterodine fumarate 8 mg.

Table 1 lists adverse events, regardless of causality, that were reported in the combined Phase 3, randomized, placebo-controlled trials at an incidence greater than placebo and in 1% or more of patients treated with fesoterodine fumarate 4 or 8 mg once daily for up to 12 weeks.

Table 1 - Adverse events with an incidence exceeding the placebo rate and reported by ≥1% of patients from double-blind, placebo-controlled Phase 3 trials of 12 weeks treatment duration

System organ class/Preferred term	Placebo N=554 %	Fesoterodine fumarate 4mg/day N=554 %	Fesoterodine fumarate 8mg/day N=566 %
Gastrointestinal disorders			
Dry mouth	7.0	18.8	34.6
Constipation	2.0	4.2	6.0
Dyspepsia	0.5	1.6	2.3
Nausea	1.3	0.7	1.9
Abdominal pain upper	0.5	1.1	0.5
Infections			
Urinary tract infection	3.1	3.2	4.2
Upper respiratory tract infection	2.2	2.5	1.8
Eye disorders			
Dry eyes	0	1.4	3.7

System organ class/Preferred term	Placebo N=554 %	Fesoterodine fumarate 4mg/day N=554 %	Fesoterodine fumarate 8mg/day N=566 %
Renal and urinary disorders			
Dysuria	0.7	1.3	1.6
Urinary retention	0.2	1.1	1.4
Respiratory disorders			
Cough	0.5	1.6	0.9
Dry Throat	0.4	0.9	2.3
General disorders			
Edema peripheral	0.7	0.7	1.2
Musculoskeletal disorders			
Back pain	0.4	2.0	0.9
Psychiatric disorders			
Insomnia	0.5	1.3	0.4
Investigations			
ALT increased	0.9	0.5	1.2
GGT increased	0.4	0.4	1.2
Skin disorders			
Rash	0.5	0.7	1.1

ALT=alanine aminotransferase, GGT=gamma glutamyltransferase

Patients also received fesoterodine fumarate for up to three years in open-label extension phases of one Phase 2 and two Phase 3 controlled trials. In all open-label trials combined, 857, 701, 529, and 105 patients received fesoterodine fumarate for at least 6 months, 1 year, 2 years, and 3 years respectively.

The adverse events observed during long-term, open-label studies were similar to those observed in the 12-week, placebo-controlled studies, and included dry mouth, constipation, dry eyes, dyspepsia and abdominal pain. Similar to the controlled studies, most adverse events of dry mouth and constipation were mild to moderate in intensity. Serious adverse events, judged to be at least possibly related to study medication by the investigator, and reported more than once during the open-label treatment period of up to 3 years included urinary retention (3 cases), diverticulitis (3 cases), constipation (2 cases), irritable bowel syndrome (2 cases), and electrocardiogram QT corrected interval prolongation (2 cases).

The safety of fesoterodine fumarate was further established in two additional 12-week, active- and placebo- controlled, double-blind, randomized studies comparing fesoterodine fumarate with tolterodine ER 4 mg and placebo. In these studies combined, 1527 patients received fesoterodine fumarate 8 mg, 1552 patients received tolterodine ER 4 mg, and 755 patients received placebo. The most common treatment- emergent adverse events (dry mouth, constipation, and headache) reported with fesoterodine fumarate during these 2 studies were similar to those observed in the

12-week, placebo-controlled studies.

In clinical trials comparing fesoterodine to placebo, cases of markedly elevated liver enzymes (ALT increased, GGT increased) were reported at a frequency no different than placebo. The relation to fesoterodine treatment is unclear.

Fesoterodine fumarate was associated with an increase in heart rate that correlated with increasing dose, a well-characterized effect described for antimuscarinic drugs. In the placebo-controlled phase 3 studies in patients with overactive bladder, the mean increases in heart rate compared to placebo were approximately 3-4 beats/minute in the 4 mg/day group and 3-5 beats/minute in the 8 mg/day group (see **ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology and Hemodynamics**).

Geriatrics (> 65 years of age):
Of 1567 patients who received fesoterodine fumarate 4mg/day or 8mg/day in the Phase 2 and 3, placebo- controlled, efficacy and safety studies, 515 (33%) were 65 years of age or older, and 140 (9%) were 75 years of age or older. No overall differences in safety or efficacy 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 8mg only) and urinary tract infection, was higher in patients 75 years of age and older as compared to younger patients.

Pediatrics (<18 years of age):

An open-label pediatric Phase 2 study with fesoterodine in overactive bladder (N=10) or neurogenic detrusor overactivity (NDO: N=11) patients aged 9 to 17 with body weight >25 kg was conducted. Patients received 4 mg once daily (N = 21) for 4 weeks, followed by dose escalation to 8 mg once daily (N = 20) for a further 4 weeks. One patient with NDO receiving fesoterodine 8 mg once daily experienced a treatment-related serious adverse event of constipation which required hospitalization and temporary discontinuation of fesoterodine. The safety and efficacy of fesoterodine fumarate in pediatric populations have not been established.

Post-Market Adverse Drug Reactions

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

Eye disorders: Blurred vision;

Cardiac disorders: Palpitations;

Central nervous system disorders: Dizziness, headache;

Skin and subcutaneous tissue disorders: Angioedema including angioedema with airway obstruction, face edema, hypersensitivity reactions, urticaria, pruritus, rash;

Renal and urinary disorders: Urinary retention.

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

DRUG INTERACTIONS

Overview

Coadministration of APO-FESOTERODINE (fesoterodine fumarate extended-release tablet) with other medicinal products with anticholinergic properties may result in more pronounced therapeutic and/or adverse effects. Fesoterodine fumarate is rapidly metabolized to active metabolite, 5-hydroxymethyl tolterodine (5-HMT), by nonspecific esterases; this active metabolite of fesoterodine is further metabolized, principally via CYP2D6 and CYP3A4. At therapeutic concentrations, 5-HMT does not inhibit CYP isoenzymes 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4 and does not induce CYP isoenzymes 1A2, 2B6, 2C9, 2C19, or 3A4.

Use With Other Concomitant Therapies:

Alpha-blockers for lower urinary tract symptoms (LUTS) in men:
Fesoterodine fumarate efficacy was not established in a study of men 40 years and older with overactive bladder symptoms taking an alpha-blocker for lower urinary tract symptoms (LUTS). No excess incidence of acute urinary retention was demonstrated. However, urinary treatment-emergent events such as urinary retention and dysuria were reported more often by men in the fesoterodine add-on group relative to the placebo add-on group (urinary retention: 2.3% versus 0.4% and dysuria: 3.2% versus 0.6%). Caution should be used when administering APO-FESOTERODINE to men with possible bladder outlet obstruction (see **WARNINGS AND PRECAUTIONS, Genitourinary**).

Drug-Drug Interactions

Table 2 - Established or Potential Drug-Drug Interactions

Proper Name	Ref	Effect	Clinical comment
Ketoconazole (potent CYP3A4 inhibitors)	CT	The effect of ketoconazole 200 mg twice daily for 5 days increased C_{max} and AUC of the active metabolite of fesoterodine by 2.0- and 2.3-fold, respectively after oral administration of fesoterodine fumarate 8 mg to CYP2D6 extensive metabolizers. In CYP2D6 poor metabolizers, the effect of ketoconazole 200 mg twice daily for 5 days increased C_{max} and AUC of the active metabolite of fesoterodine by 2.1- and 2.5-fold, respectively. Furthermore, in subjects who were CYP2D6 poor metabolizers and taking ketoconazole versus subjects who were CYP2D6 extensive metabolizers and not taking ketoconazole, the C_{max} and	Dose of fesoterodine greater than 4 mg are not recommended in patients taking potent CYP3A4 inhibitors such as ketoconazole, itraconazole, miconazole and clarithromycin

Proper Name	Ref	Effect	Clinical comment
		AUC increased by 4.5 and 5.7 fold, respectively. The effect of ketoconazole 200 mg once a day for 5 days increased C_{max} and AUC of the active metabolite of fesoterodine by 2.2-fold in CYP2D6 extensive metabolizers and 1.5- and 1.9- fold, respectively, in CYP2D6 poor metabolizers. Furthermore, in subjects who were CYP2D6 poor metabolizers and taking ketoconazole versus subjects who were CYP2D6 extensive metabolizers and not taking ketoconazole, the C_{max} and AUC increased by 3.4 and 4.2 fold, respectively.	
Fluconazole (moderate CYP3A4 inhibitors)	CT	Co-administration of fesoterodine 8mg with fluconazole 200 mg twice daily increased C_{max} and AUC_{inf} of the active metabolite of fesoterodine by approximately 19% (11% - 28%) and 27% (18% - 36%), respectively.	The increase in the active metabolite of fesoterodine is not considered clinically relevant. No dosage adjustment is recommended when fesoterodine is co-administered with a moderate CYP3A4 inhibitor.
Cimetidine (Weak CYP3A4 inhibitors)	T	The effect of weak CYP3A4 inhibitors was not examined; it is not expected to be in excess of the effect of moderate inhibitors.	
Rifampicin (CYP3A4 inducers)	CT	Following induction of CYP3A4 by 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 fesoterodine 8 mg. The terminal half- life of the active metabolite was not changed.	Induction of CYP3A4 may lead to reduced plasma levels of the active metabolite of fesoterodine. No dosing adjustments are recommended in the presence of CYP3A4 inducers such as rifampicin or carbamazepine. However, concomitant use of CYP3A4 inducers is not recommended.
CYP2D6 inhibitors	T	In poor metabolizers for CYP2D6, C_{max} and AUC of the active metabolite were increased 1.7- and 2-fold, respectively.	The interaction with CYP2D6 inhibitors was not tested clinically. No dosing adjustments are recommended in the presence of CYP2D6 inhibitors.
Warfarin	CT	A clinical study has shown in healthy volunteers that fesoterodine 8 mg once daily has no significant effect on the PK or the anticoagulant activity of a single 25 mg dose of warfarin. Standard therapeutic monitoring for warfarin should be continued.	
Oral contraceptives	CT	In the presence of fesoterodine, there were no clinically significant changes in the plasma concentrations of combined oral contraceptives	

Proper Name	Ref	Effect	Clinical comment
		containing 0.03 mg ethinyl estradiol and 0.15mg levonorgestrel	

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Drug-Food Interactions

Fesoterodine tablets can be taken with or without food. There is no clinically relevant effect of food on the pharmacokinetics of fesoterodine. Concomitant food intake increased the active metabolite of fesoterodine AUC by 19% and C_{max} by 18% (see **DOSAGE AND ADMINISTRATION)**.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Dosing of APO-FESOTERODINE (fesoterodine fumarate) may be affected by the following:

- Individual response and tolerability
- Impaired hepatic function and renal impairment
- Potent CYP3A4 inhibitors

(See **WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment.**)

Recommended Dose and Dosage Adjustment

The recommended starting dose of APO-FESOTERODINE is 4 mg once daily.
Based upon individual response and tolerability, the dose may be increased to 8 mg once daily.

The daily dose of APO-FESOTERODINE should not exceed 4 mg in the following populations:

- Patients with severe renal impairment (CLCR < 30 mL/min)
- Patients taking potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, miconazole, and clarithromycin.

APO-FESOTERODINE is not recommended for use in patients with severe hepatic impairment (Child-Pugh C). Dosage adjustment may not be necessary for elderly patients (≥ 65 years of age) (see **WARNINGS AND PRECAUTIONS - Special Populations)**.

Administration

APO-FESOTERODINE tablets should be taken with liquid and swallowed whole. APO-FESOTERODINE can be administered with or without food, and should not be chewed, divided, or crushed. APO-FESOTERODINE may be taken during the day or at night (see **ACTION AND CLINICAL PHARMACOLOGY Pharmacokinetics – Daytime versus Nighttime**).

OVERDOSAGE

Overdosage with fesoterodine could result in severe antimuscarinic effects and should be treated accordingly.

Treatment of overdosage with fesoterodine should consist of gastric lavage and activated charcoal. Treatments for symptoms are recommended as follows. For severe central anticholinergic effects (hallucinations, severe excitation), an anticholinesterase agent, such as physostigmine, may be used. If excitation and convulsions occur, administer an anticonvulsant, such as diazepam. Patients with respiratory insufficiency should be given respiratory assistance. If respiratory arrest occurs, patients should be given artificial respiration. Patients with tachycardia may be treated with a beta-blocker, and those with urinary retention may be catheterized. Patients with troublesome mydriasis may be placed in a dark room or treated with pilocarpine eye drops, or both. ECG should be monitored.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Fesoterodine is a unique competitive muscarinic receptor antagonist. After oral administration, fesoterodine is rapidly and extensively hydrolyzed by nonspecific esterases to its active metabolite, 5-hydroxymethyl tolterodine (5-HMT), which is responsible for the antimuscarinic activity of fesoterodine. The conversion of fesoterodine fumarate to its active metabolite is not dependent on cytochrome P450 enzymes.

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.

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.

Cardiac Electrophysiology and Hemodynamics

The effect of fesoterodine 4 mg (therapeutic dose) and 28 mg (supratherapeutic dose) on the ECG parameters was evaluated in a double-blind, randomized, placebo- and positive-controlled (moxifloxacin 400 mg once a day) parallel group 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. The study demonstrated that fesoterodine at doses of 4 and 28 mg/day did not prolong the QTc interval, the QRS duration, or the PR interval in a treatment related manner.

Fesoterodine fumarate was associated with an increase in heart rate that correlated with increasing dose, a well-characterized effect described for antimuscarinic drugs. On day 3 of the study described above, when compared to placebo, the mean increases in heart rate averaged over 24 h, were 3 beats/minute for 4 mg/day fesoterodine and 11 beats/minute for 28 mg/day fesoterodine (see **ADVERSE REACTIONS**).

Routine safety monitoring in this study included blood pressure assessment. On day 3 of treatment, blood pressure measurements were performed at 4-5 h post-dosing. Mean changes from baseline in systolic blood pressure were -1.9 mmHg (90% CI: -4.0, 0.1) with fesoterodine 4 mg/day, 0.3 mmHg (90% CI: -2.4, 2.9) with fesoterodine 28 mg/day, and -3.8 mmHg (90% CI -6.1, -1.5) with placebo. Mean changes from baseline in diastolic blood pressure were 1.4 mmHg (90% CI: -0.2, 3.1) with fesoterodine 4 mg/day, 3.7 mmHg (90% CI: -1.9, 5.4) with fesoterodine 28 mg/day, and -2.9 mmHg (90% CI -4.7, -1.1) with placebo. In phase 3 controlled clinical trials, systolic and diastolic blood pressure was assessed at steady state at each clinic visit. No difference from placebo was observed with fesoterodine at either 4mg/day or 8mg/day.

Cognitive Testing in Healthy Elderly

A phase I, 4-treatment, cross-over, double-blind, placebo- and positive-controlled study in elderly healthy volunteers (n=20, mean age 72 years) evaluated the effect of fesoterodine 4 mg and 8 mg, placebo and alprazolam 1 mg (positive control) on a computer-based battery of cognitive tests and memory tests (CogState Tests: comprised of a detection task, an identification task, a one-card learning task, a continuous paired associate learning task, and the Groton maze learning task) and the Rey Auditory Verbal Learning Tests (RAVLT). There were no statistically significant differences between fesoterodine 4 mg and placebo (p=0.1198) or between fesoterodine 8 mg and placebo (p=0.2459) for the primary endpoint (CogState detection task). The validity of the study assessment was confirmed by the results of the positive control. Similar results were obtained for all other pharmacodynamics endpoints, including the battery of Rey Auditory Verbal Learning Tests, which were similarly statistically non-significant between fesoterodine and placebo.

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 (5-HMT), fesoterodine cannot be detected in plasma. Bioavailability of the active metabolite 5-HMT 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 (5-HMT) after a single dose of fesoterodine fumarate 4 mg and 8 mg in extensive and poor metabolizers of CYP2D6 from subjects in a fasted state is provided in Table 3.

Table 3 - Summary of geometric mean [CV] pharmacokinetic parameters for the active metabolite (5-HMT) after a single dose of fesoterodine fumarate 4 mg and 8 mg in extensive and poor CYP2D6 metabolizers from subjects in a fasted state

Parameter	Fesoterodine fumarate 4 mg EM (n=16)	PM (n=8)	Fesoterodine fumarate 8 mg 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	7.31	8.59	7.66

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)

Distribution: Plasma protein binding of the active metabolite 5-HMT is low (approximately 50%) and is 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 5-HMT. 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. 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 apparent terminal half-life following oral administration is approximately 7 hours.

Daytime versus Nighttime: APO-FESOTERODINE may be taken during the day or at night. In a randomized, open-label, 2-period, 2-treatment crossover, single-dose study of fesoterodine fumarate 8 mg tablets in healthy subjects, the relative bioavailability of the active metabolite of fesoterodine, as measured by AUC_{inf} ratio, was estimated to be about 93%, and the 90% CI was contained entirely within the bioequivalence limits of 80% to 125%. The C_{max} ratio was

estimated to be about 78%.

When compared to daytime dosing, the modest lowering of C_{max} at nighttime is unlikely to be of clinical relevance for antimuscarinic efficacy.

Effect of Food: There is no clinically relevant effect of food on the pharmacokinetics of fesoterodine (see **DOSAGE AND ADMINISTRATION**). 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 C_{max} by 18%.

Special Populations and Conditions

Pediatrics: An open-label pediatric Phase 2 pharmacokinetic study with fesoterodine was conducted in 21 patients. Efficacy and safety of fesoterodine in the pediatric population have not been established. Therefore, fesoterodine should not be used in pediatric patients (see **ADVERSE REACTIONS, Clinical Adverse Drug Reactions, Pediatric (< 18 years of age)**).

Geriatrics: The pharmacokinetics of fesoterodine was not significantly influenced by age (see DOSAGE AND ADMINISTRATION).

Gender: The pharmacokinetics of fesoterodine was not significantly influenced by gender (see DETAILED PHARMACOLOGY).

Race: The pharmacokinetics of fesoterodine was not significantly influenced by race (see DETAILED PHARMACOLOGY).

Renal Impairment: In patients with mild or moderate renal impairment (CL_{CR} ranging from 30-80 mL/min), C_{max} and AUC of the active metabolite 5-HMT were increased up to 1.5- and 1.8-fold respectively, as compared to healthy subjects. In patients with severe renal impairment (CL_{CR} < 30 mL/min), C_{max} and AUC were increased 2.0- and 2.3-fold, respectively.

In patients with mild or moderate renal impairment, no dose adjustment is required. Doses of APO-FESOTERODINE greater than 4 mg are not recommended in patients with severe renal impairment (see **WARNINGS AND PRECAUTIONS – Renal** and **DOSAGE AND ADMINISTRATION** sections).

Hepatic Impairment: In patients with moderate (Child-Pugh B) hepatic impairment, C_{max} and AUC of the active metabolite were 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 APO-FESOTERODINE is not recommended for use in these patients (see **WARNINGS AND PRECAUTIONS – Hepatic/Biliary/Pancreatic** and **DOSAGE AND ADMINISTRATION** sections).

STORAGE AND STABILITY

Store between 15°C to 25°C. Protect from light and moisture.

DOSAGE FORMS, COMPOSITION AND PACKAGING

APO-FESOTERODINE (fesoterodine fumarate extended-release tablets) is available as 4 mg tablets (light blue colored, oval-shaped biconvex, film coated tablet engraved with “APO” on one side and “F4” on other side), and 8 mg tablets (blue colored, oval-shaped biconvex, film coated tablet engraved with “APO” on one side and “F8” on other side) and are supplied as follows:

- Bottles of 100 tablets

The tablets also contain the following inactive ingredients:
Colloidal silicon dioxide, glyceryl behenate, hypromellose, indigotine AL lake, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Fesoterodine fumarate

Chemical name:

1. 2-((1*R*)-3-(bis(1-methylethyl)amino)-1-phenylpropyl)-4-(hydroxymethyl)phenyl 2-methylpropanoate hydrogen (2*E*)-butenedioate (salt)

2. 2-((1*R*)-3-(Diisopropylamino)-1-phenylpropyl)-4-(hydroxymethyl)phenyl isobutyrate

3. 2-((1*R*)-3-(bis(1-methylethyl)amino)-1-phenylpropyl)-4-(hydroxymethyl)phenyl 2-methylpropanoate hydrogen (2*E*)-butenedioate (salt)

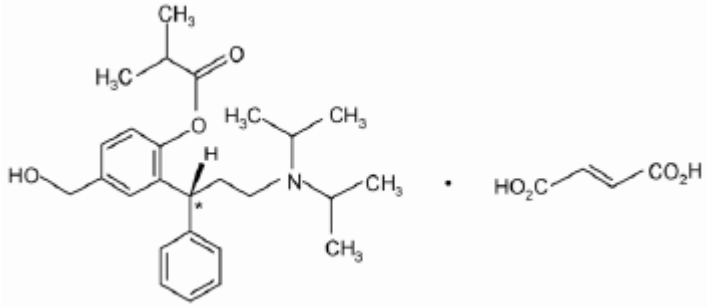
4. Isobutyric acid 2-((R)-3-diisopropylammonium-1-phenylpropyl)-4-(hydroxymethyl)phenyl ester hydrogen fumarate (IUPAC)

CAS Name: Propanoic acid, 2-methyl, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester, (2E)-2- butenedioate (1:1) (salt)

CAS Number: 286930-03-8

Molecular formula: $C_{30}H_{41}NO_7$

Molecular mass: 527.65 g/mol (salt); 411.58 g/mol (base) Structural formula:



*The asterisk designates the chiral centre

Physicochemical properties:

Appearance: Fesoterodine fumarate is a white to off-white powder.
Melting Point: The typical melting point is 105°C to 111°C.
pKa: Fesoterodine: pKa = 10.31 ± 0.01, at 23.4°C.
Dibasic fumaric acid: $pK_{a,1}$=2.94, $pK_{a,2}$=4.46 at 20 °C
pH: The pH of aqueous solution at 1% (w/v) varies between 3.5 and 3.6 at 20°C.
Solubility:

Solvent	Solubility
Water	Freely soluble
Ethyl alcohol	Soluble
Methanol	Soluble
Acetic acid	Sparingly soluble
Isopropyl alcohol	Sparingly soluble
Propylene glycol	Soluble
Acetone	Sparingly soluble
DMF	Soluble
DMSO	Soluble
Acetonitrile	Sparingly soluble
Toluene	Vety slightly soluble
Heptane	Very slightly soluble
pH 1.2 Buffer	Very soluble
pH 4.5 Buffer	Very soluble
pH 6.8 Buffer	Very soluble
pH 8.0 Buffer	Very soluble

CLINICAL TRIALS

Comparative Bioavailability Studies

Fasting:

A randomized, single-dose, two-way crossover comparative bioavailability study of APO-Fesoterodine 8 mg ER Tablets (Apotex Inc.) and Toviaz$^{TM/MC}$ 8 mg ER Tablets (Pfizer Canada Inc.) was conducted in healthy volunteers under fasting conditions. Comparative bioavailability data, based on the active metabolite of fesoterodine, 5-hydroxy methyl tolterodine, from 42 subjects that were included in the statistical analysis are presented in the following table.

SUMMARY TABLE OF COMPARATIVE BIOAVAILABILITY DATA

5-Hydroxy Methyl Tolterodine (1 x 8 mg fesoterodine) Geometric mean Arithmetic Mean (CV%)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval (%)
AUC_T (pg•h/mL)	50095.8 53579.1 (37.7)	53387.2 56223.1 (32.6)	93.8	89.9 - 97.9
AUC_I (pg•h/mL)	50843.8 54289.1 (37.3)	54099.1 56908.0 (32.3)	94.0	90.1 - 98.0
C_{max} (pg/mL)	3958.5 4208.6 (37.3)	4504.2 4715.9 (30.8)	87.9	83.0 - 93.0
T_{max}[§] (h)	5.00 (2.50 – 7.00)	5.00 (3.50 – 7.00)		
$T_{1/2}$[#] (h)	5.56 (28.8)	6.13 (24.3)		
* APO-Fesoterodine (fesoterodine fumarate) extended release tablets, 8 mg (Apotex Inc.) † Toviaz™/MC (fesoterodine fumarate) extended release tablets, 8 mg (Pfizer Canada Inc.) § Expressed as median (range) # Expressed as arithmetic mean (CV%) only.				

Fed:

A randomized, single-dose, two-way crossover comparative bioavailability study of APO-Fesoterodine 8 mg ER Tablets (Apotex Inc.) and Toviaz™/MC 8 mg ER Tablets (Pfizer Canada Inc.) was conducted in healthy volunteers under fed conditions. Comparative bioavailability data, based on the active metabolite of fesoterodine, 5-hydroxy methyl tolterodine, from 40 subjects that were included in the statistical analysis are presented in the following table.

SUMMARY TABLE OF COMPARATIVE BIOAVAILABILITY DATA

5-Hydroxy Methyl Tolterodine (1 x 8 mg fesoterodine) Geometric mean Arithmetic Mean (CV%)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval (%)
AUC_T (pg•h/mL)	55552.6 57351.8 (25.3)	60869.7 63028.9 (27.7)	91.3	87.5- 95.2
AUC_I (pg•h/mL)	56292.5 58135.9 (25.5)	61503.2 63678.4 (27.7)	91.5	87.7- 95.5
C_{max} (pg/mL)	4694.5 4870.7 (27.7)	5687.2 5866.1 (24.6)	82.5	78.4- 86.9

T_{max}[§] (h)	4.50 (1.50 – 10.08)	5.00 (2.50 – 8.00)		
$T_{1/2}$[#] (h)	5.48 (38.2)	5.48 (32.8)		

* APO-Fesoterodine (fesoterodine fumarate) extended release tablets, 8 mg (Apotex Inc.)

† Toviaz™/MC (fesoterodine fumarate) extended release tablets, 8 mg (Pfizer Canada Inc.)

§ Expressed as median (range)

#Expressed as arithmetic mean (CV%) only.

Study Demographics and Trial Design

The efficacy of fixed doses of fesoterodine 4 mg and 8 mg taken orally once daily was evaluated in two Phase 3 randomized, double-blind, placebo-controlled, 12-week studies. The co-primary endpoints were the change from Baseline to Week 12 in the average number of micturitions per 24 hours and a change from Baseline to Week 12 in the average number of UUI episodes per 24 hours (US analysis) or treatment response derived from the Treatment Benefit Scale (European analysis). Secondary endpoints included change in mean voided volume, daytime micturitions, urgency episodes per 24 hours, number of continent days per week, and change in severity of urgency episodes. A summary of the Patient Demographics for Study 1 and 2 is provided in Table 4.

Table 4 - Summary of Patient Demographics for Study 1 and Study 2

Study # (Country or region)	Trial design	Dosage	Study subjects	Mean age (Range)	Gender	Race
Study 1 (Europe, Australia, New Zealand, South Africa)	Randomized, double-blind, double-dummy, placebo- and active-controlled, parallel-arm	Fesoterodine 4 mg Fesoterodine 8 mg Placebo Tolterodine ER	N=272 N=288 N=285 N=290	57 years (19-86)	81 % F 19 % M	97 % White
Study 2 (USA)	Randomized, double-blind, placebo-controlled, parallel-arm	Fesoterodine 4 mg Fesoterodine 8 mg Placebo	N= 283 N= 279 N= 274	59 years (21-91)	76 % F 24 % M	82 % White 9 % Black 8% Other

F= Female; M=Male

Study Results

Fesoterodine-treated patients had statistically significant mean reductions in the number of micturitions per 24 hours and in the number of urge incontinence episodes per 24 hours at the end of treatment compared with placebo-treated patients. Likewise, the response rate (% of patients reporting that their condition has been "greatly improved" or "improved" using a 4-point Treatment Benefit Scale) was significantly greater with fesoterodine compared with placebo.

Furthermore, fesoterodine improved the mean change in the voided volume per micturition, and the mean change in the number of continent days per week (see Table 5).

Table 5 - Mean Changes from Baseline to End of Treatment for Primary and Selected Secondary Endpoints

Parameter	Study 1				Study 2		
	Placebo	Feso 4 mg	Feso 8 mg	Tolterodine ER 4 mg	Placebo	Feso 4 mg	Feso 8 mg
Number of micturitions per 24 hours [#]							
	N=279	N=265	N=276	N=283	N=266	N=267	N=267
Baseline	12.0	11.6	11.9	11.5	12.2	12.9	12.0
Change from Baseline	-1.02	-1.74	-1.94	-1.69	-1.02	-1.86	-1.94
p-value vs Pbo	-	<0.001	<0.001	0.001	-	0.032	<0.001
Responder rate[#] (treatment response)							
	N=279	N=265	N=276	N=283	N=266	N=267	N=267
Responder rate	53.4%	74.7%	79.0%	72.4%	45.1%	63.7%	74.2%
p-value vs Pbo	-	<0.001	<0.001	<0.001	-	<0.001	<0.001
Number of urge incontinence episodes per 24 hours [#]							
	N=211	N=199	N=223	N=223	N=205	N=228	N=218
Baseline	3.7	3.8	3.7	3.8	3.7	3.9	3.9
Change from Baseline	-1.20	-2.06	-2.27	-1.83	-1.00	-1.77	-2.42
p-value vs Pbo	-	0.001	<0.001	0.008	-	0.003	<0.001
Number of continent days per week							
	N=211	N=199	N=223	N=223	N=205	N=228	N=218
Baseline	0.8	0.8	0.6	0.6	0.6	0.7	0.7
Change from Baseline	2.1	2.8	3.4	2.5	1.4	2.4	2.8
p-value vs Pbo	-	0.007	<0.001	0.139	-	<0.001	<0.001
Voided volume per micturition (ml)							
	N=279	N=265	N=276	N=283	N=266	N=267	N=267
Baseline	150	160	154	154	159	152	156
Change from Baseline	10	27	33	24	8	17	33
p-value vs Pbo	-	<0.001	<0.001	0.002	-	0.150	<0.001

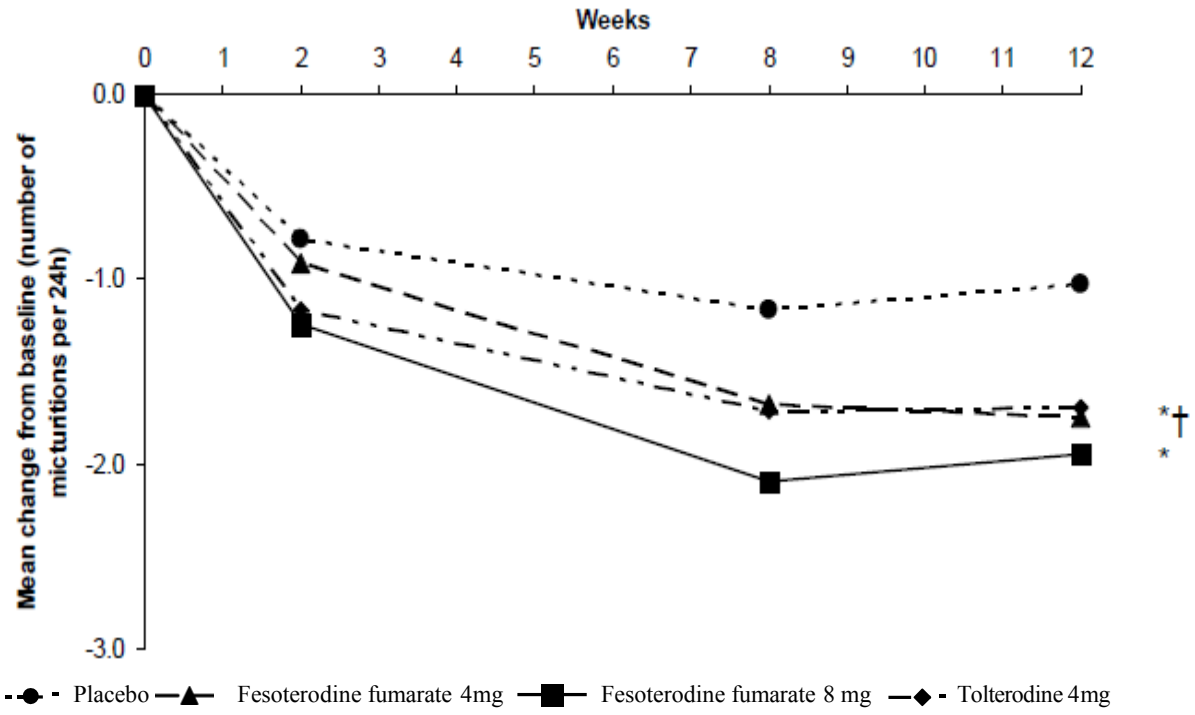
The values are the mean change from baseline and the p-values represent the difference in LS mean vs Placebo.

[#] primary end points; Feso=fesoterodine
vs=versus; Pbo= placebo

In addition, sustained efficacy was shown during a 3-year open-label extension of one phase 2 and 2 phase 3 studies. Long-term treatment with fesoterodine resulted in maintained or continued improvement in all efficacy and health-related quality of life measures.

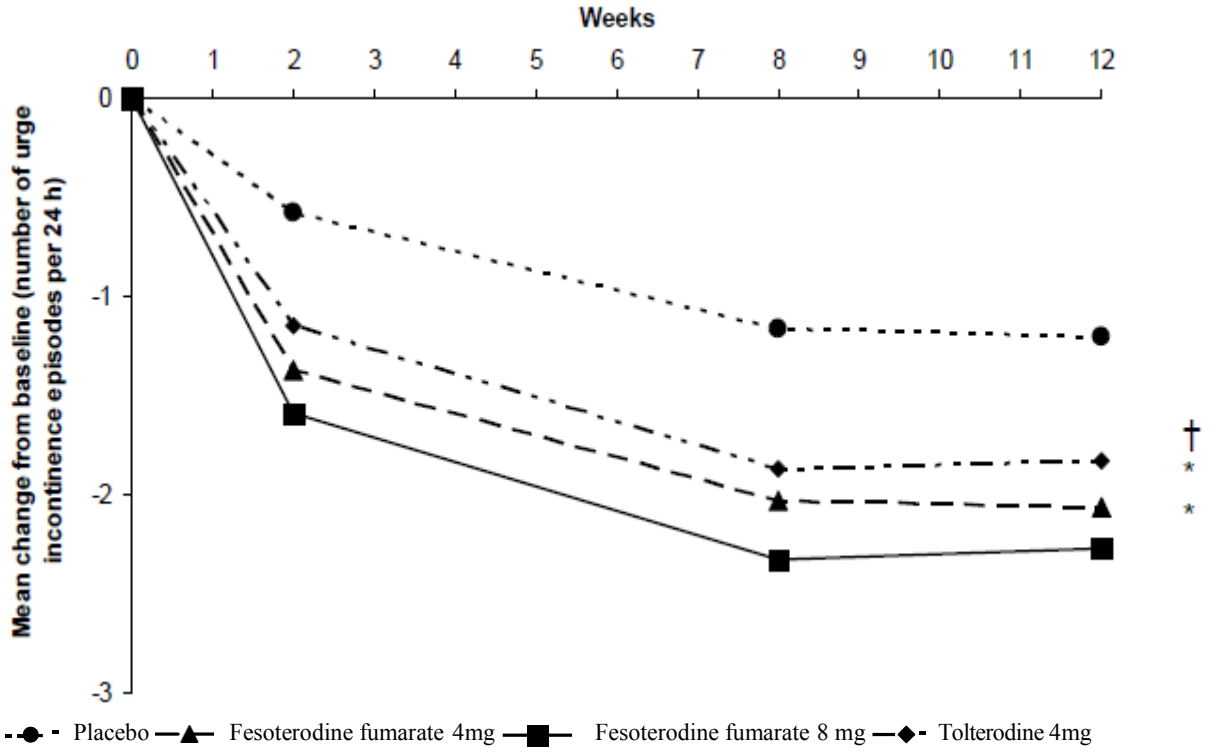
Figures 1-4: The following figures show change from baseline over time in number of micturitions and urge urinary incontinence episodes per 24 hours in the two Phase 3 studies (Study 1 and Study 2, respectively).

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



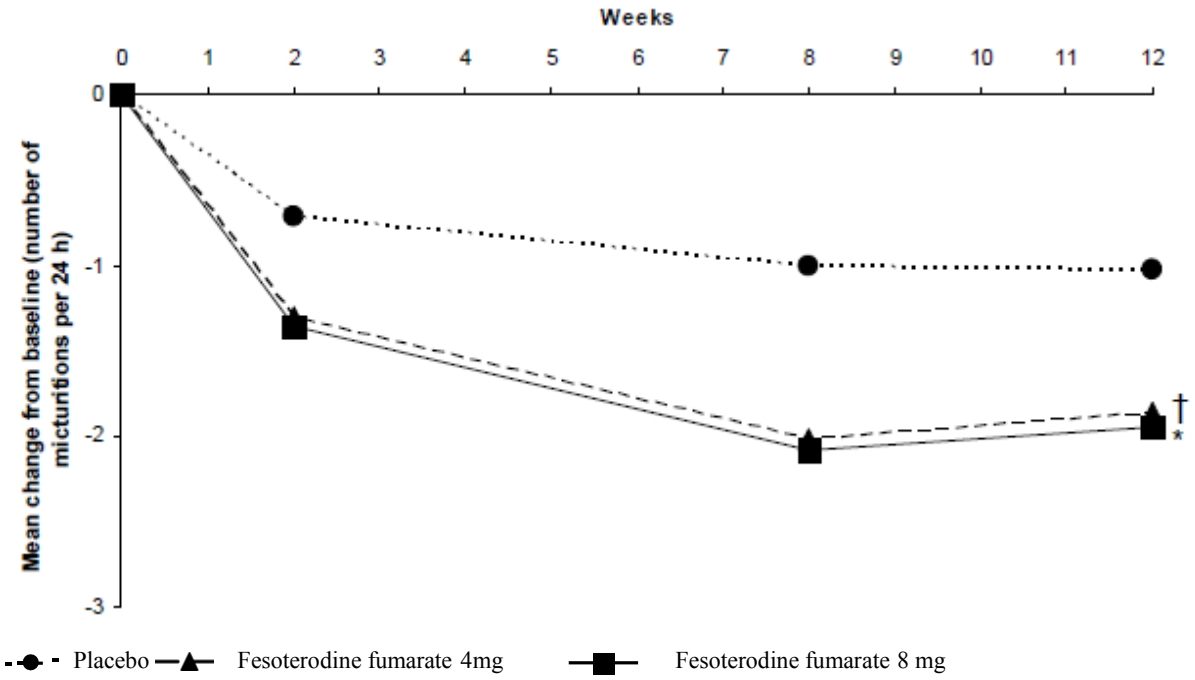
p-values vs Placebo: * p<0.001 for Fesoterodine fumarate 4 mg and 8 mg;
†p=0.001 for tolterodine ER 4mg

Figure 2 - Change in Urge Incontinence episodes per 24h (Study 1)



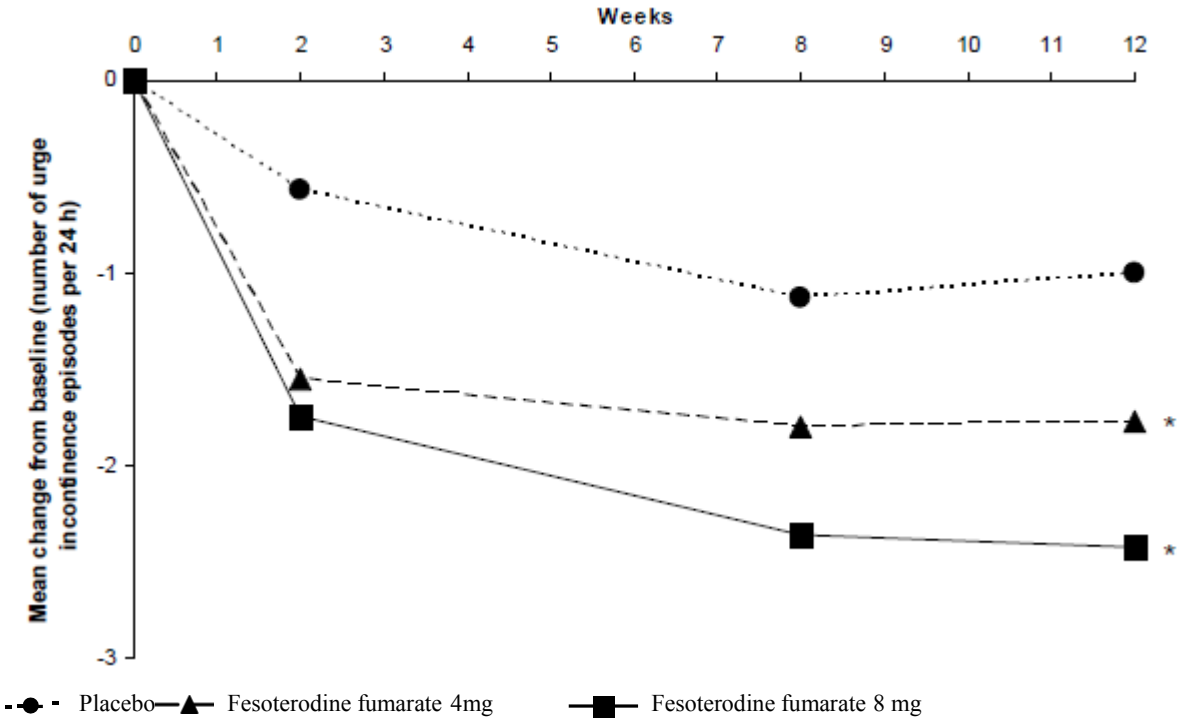
p-values vs Placebo: * p<0.001 for Fesoterodine fumarate 4 mg and 8 mg; †p=0.008 for tolterodine ER 4mg

Figure 3 - Number of Micturitions per 24h (Study 2)



P-values vs Placebo: * p<0.001 for Fesoterodine fumarate 8 mg; †p=0.032 for Fesoterodine fumarate 4mg

Figure 4 - Change in Urge Incontinence Episodes per 24h (Study 2)



P-values vs Placebo: * p<0.001 for Fesoterodine fumarate 4mg and 8 mg

DETAILED PHARMACOLOGY

Non-clinical Pharmacology

In Vitro

The in vitro binding and functional studies demonstrate that fesoterodine and its primary in vivo active metabolite (5-HMT or SPM7605) are specific but non-selective muscarinic receptor antagonist. In vivo, fesoterodine is rapidly and extensively metabolized to its active metabolite (5-HMT), which is much more potent and active than fesoterodine. As the further metabolites of 5-HMT are less potent and active, 5-HMT is the main active metabolite in vivo.

A study investigated the permeability of 5-HMT (the active metabolite of fesoterodine), oxybutynin, fesoterodine, tolterodine, solifenacin, darifenacin, and trospium across the blood brain barrier (BBB) using porcine brain endothelial cells monolayers as an in vitro model of the BBB. The results of the study demonstrated that 5-HMT had a 3.6 to 5.5 fold lower likelihood of crossing the BBB compared with 5 of the 6 other compounds (trospium being the only one less likely than 5-HMT to cross the BBB). The study also used cyclosporine A to identify the potential of the seven compounds to be transported out of the brain by P-glycoprotein (P-gp).
P-gp is a membrane transporter of brain capillaries that transports molecules out of the brain and back into the blood. Although the physical properties of 5-HMT suggest that it would have a moderate/high potential to cross the BBB, no significant CNS penetration was observed in rats. This is likely due to P-gp catalyzed efflux of the drug. 5-HMT is a substrate of P-gp, which would transport 5-HMT back out of the brain.

In Vivo

The effects of fesoterodine and its main active metabolite 5-HMT (or SPM7605) on urodynamic parameters were assessed in the cystometry model in conscious rats. Intravenous administration of both compounds significantly reduced micturition pressure by more than 60% at doses as low as 10 µg/kg, and bladder capacity and intercontraction intervals were increased. At higher doses these effects disappeared and even the opposite was noted. Qualitatively similar effects were obtained with tolterodine, oxybutynin and atropine. No significant effects were observed on basal pressure, threshold pressure, micturition volume and residual volume.

Another study investigated the effects of the antimuscarinic drugs after intravenous infusion at lower doses in a similar rat model. Intravenous infusion of the test compounds produced a dose dependent inhibition of the intravesical volume-induced urinary bladder contractions measured as the micturition pressure with an ID50 of 22 nmol/kg and 94 nmol/kg iv for 5-HMT and tolterodine, respectively. No effects were observed on the micturition number, micturition volume, residual volume or bladder capacity.

In cats, 5-HMT dose-dependently inhibited the acetylcholine-induced contractions of the bladder (ID50 5.1 µg/kg) and the electrically stimulated salivation (ID50 13.7 µg/kg). This indicates that 5-HMT (or SPM 7605) is three times more potent to interfere with events in the urinary bladder compared to the salivary gland in cats.

Studies to assess effects on the central nervous system in female mice showed that single oral doses of 10 and 30 mg/kg fesoterodine gave dose-dependent effects on clinical observations in a modified Irwin test in which qualitative increases in spontaneous locomotor activity, touch and pain response and respiratory rate as well as restlessness, aggression and mydriasis were observed. Other studies using the same doses of fesoterodine showed no effects on spontaneous locomotor activity (quantitative assessment) or hexobarbital sleeping time nor exerted any pro- or anti-convulsant activity in mice. When compared to the human therapeutic dose of 8 mg once daily, the margins for the doses of 10 mg/kg and 30 mg/kg are 90-fold and 270-fold, respectively.

Supra-therapeutic concentrations of fesoterodine and 5-HMT have been shown to reduce K^+ channel current in human embryonic kidney (HEK293) cells expressing human ether-a-go-go-related gene (hERG), and prolong action potential duration in canine isolated Purkinje fibres. In vivo, in the anaesthetised dog, intravenous bolus administration of 80 and 800 µg/kg of fesoterodine resulted in increases in the QTc interval of 2% and 11%, respectively. However, in conscious dogs, fesoterodine administered orally at doses up to 12.5 mg/kg/day for 9 months had no effect on either the QT or QTc interval. Resulting mean unbound plasma C_{max} of 5-HMT in both male and female dogs corresponded to 125-fold the mean unbound plasma C_{max} (4.05 ng/ml) in fed human poor CYP2D6 metabolizers after fesoterodine 8 mg once daily.

Clinical Pharmacokinetics - Special Populations:

Gender
Following a single 8 mg oral dose of fesoterodine, the mean (+/-SD) AUC and C_{max} for the active metabolite of fesoterodine in 12 elderly men (mean age 67 years) were 51.8 +/- 26.1 h*ng/mL and 3.8 +/- 1.7 ng/mL, respectively. In the same study, the mean (+/-SD) AUC and C_{max} in 12 elderly women (mean age 68 years) were 56.0 +/- 28.8 h*ng/mL and 4.6 +/- 2.3 ng/mL, respectively.

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 C_{max} for the active metabolite of fesoterodine in Caucasian males were 73.0 +/- 27.8 h*ng/mL and 6.1 +/- 2.7 ng/mL, respectively. The mean (+/- SD) AUC and C_{max} in Black males were 65.8 +/- 23.2 h*ng/mL and 5.5 +/- 1.9 ng/mL, respectively. In single- and multiple-dose studies in Japanese and Korean young male volunteers, following administration of 4 and 8 mg fesoterodine, the AUC and C_{max} of the active metabolite of fesoterodine increased in proportion with dose, and were similar to those in Western studies.

TOXICOLOGY

Toxicological studies have been performed in mice, rats, rabbits and dogs. The selection of the species is justified by in vitro and in vivo metabolism studies. The local tolerance was tested in guinea-pigs and rabbits. In all studies, except the acute oral and intravenous toxicity studies in mice and rats and some dose-range finding studies, negative control groups have been employed. Adequate positive control substances have proven the integrity of the genotoxicity test-battery, the skin sensitization test and the immuno-toxicology study.

Single-Dose Toxicity

The NOEL and LD50 for both mice and rats were 100 and ≥ 316 mg/kg following oral administration, and 10 and 31.6 mg/kg after intravenous administration of fesoterodine.

Repeat-Dose Toxicity

Rodent
In rodents, the signs of toxicity were different in mice and rats after oral administration of fesoterodine. The NOEL was 5 mg/kg in both species after 13 weeks and in mice after 26 weeks of treatment.

Dogs
No mortality occurred in dogs after oral treatment with 0, 0.5, 2.5 or 10 mg/kg fesoterodine for 13-weeks or 0, 0.5, 2.5 or 12.5 mg/kg fesoterodine for 9-months. No overt toxicity was noted and no fesoterodine-specific target organs could be identified. Mainly antimuscarinic effects were observed in the form of reduced lacrimal secretion leading to conjunctivitis in the high dose groups, a tightly filled gall bladder due to sphincter closure (after 9 months) and an increased heart rate starting at 2.5 mg/kg (dose dependent in females). No changes in the electrical complexes of the ECG were seen. In addition, the body weights were reduced in the males starting at 2.5 mg/kg and in the females in the high dose group in the 9-month study. Clinical hematology and biochemistry revealed increased platelet counts and urea concentration in blood in the high-dosed animals. All noted test-substance related effects were reversible after a 4-week recovery period. The NOEL was 0.5 mg/kg in these studies, and the NOAEL was 2.5 mg/kg.

Carcinogenicity
No evidence of drug-related carcinogenicity was found in 24-month studies with oral administration to mice and rats. The unbound AUC of 5-HMT at the highest tolerated dose in mice corresponded to 17 to 31 times (females) and 6 to 15 times (males) the unbound human 5- HMT AUC value (46.2 ng*h/mL) in fed human poor CYP2D6 metabolizers reached with fesoterodine 8 mg, which is the Maximum Recommended Human Dose (MRHD). In rats, the unbound 5-HMT AUC at the highest tolerated dose corresponded to 4 to 13 times (females) and 6 to 24 times (males), the unbound human 5-HMT AUC (46.2 ng*h/mL) in fed human poor CYP2D6 metabolizers at the MRHD.

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

Reproduction and Teratology
Fesoterodine had no effect on male reproductive function or fertility in mice at doses up to 45 mg/kg/day. 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 a dose of 45 mg/kg/day, the resulting exposures are approximately 5 to 19 times (based on lowest and highest total systemic exposure) those at the MRHD, 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 continuing through Day 7 of gestation. Reproduction studies have shown minor embryotoxicity (increased number of resorptions, pre-implantation and post- implantation losses). At the NOEL, based on human unbound 5-HMT AUC in the fed state (46.2 ng*h/mL), the unbound systemic exposure was 1 to 2.4 times higher in mice than in humans at the MRHD, whereas based on peak plasma concentrations, the unbound exposure in mice was 8 to 15 times higher. The Lowest-Observed-Effect Level (LOEL) for maternal toxicity was 45 mg/kg/day.

No dose-related teratogenicity was observed in reproduction studies performed in mice and rabbits. In mice treated at 7-30 times the human MRHD (45mg/kg/day, oral; based on unbound 5-HMT AUC in comparison to fed human poor metabolizers at 8 mg fesoterodine), decreased live fetuses and reduced F1 fetal body weight 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 6 to 18 times the human MRHD (27 mg/kg/day, oral; based on unbound AUC comparison to human poor metabolizers at 8 mg fesoterodine), incompletely ossified sternebrae (retardation of bone development) were observed in fetuses. 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.

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30. Product Monograph - TOVIAZ® (Fesoterodine fumarate extended-release tablets) 4 mg and 8 mg. Pfizer Canada Inc., Date of Revision: December 13, 2017, Control Number: 202700.

IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

Pr APO-FESOTERODINE

Fesoterodine Fumarate Extended-Release Tablets

This leaflet is part III of a three-part "Product Monograph" published when APO-FESOTERODINE (fesoterodine fumarate) was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about APO-FESOTERODINE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

The name of this medication is **APO-FESOTERODINE.** It is used for the treatment of the symptoms of overactive bladder which include frequency, urgency, and urge incontinence or any combinations of these symptoms.

What it does:

APO-FESOTERODINE works to prevent bladder contractions or spasms. This results in more bladder capacity and less frequency, urgency and involuntary loss of urine.

When it should not be used:

You should **not take APO-FESOTERODINE** if you have:

- urinary retention,
- gastric retention
- eye problem called uncontrolled-narrow angle glaucoma,
- known hypersensitivity to fesoterodine fumarate, tolterodine L-tartrate tablets, tolterodine L-tartrate extended-release capsules, or any of the ingredients in **APO-FESOTERODINE**.

What the medicinal ingredient is:

Fesoterodine fumarate.

What the nonmedicinal ingredients are:

Colloidal silicon dioxide, glyceryl behenate, hypromellose, indigotine AL lake, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

What dosage forms it comes in:

APO-FESOTERODINE 4 mg extended-release tablets (light blue colored, oval-shaped biconvex, film coated tablet engraved with “APO” on one side and “F4” on other side)

APO-FESOTERODINE 8 mg extended-release tablets (blue colored, oval-shaped biconvex, film coated tablet engraved with “APO” on one side and “F8” on other side)

WARNINGS AND PRECAUTIONS

BEFORE you use APO-FESOTERODINE talk to your doctor or pharmacist if:

- you are pregnant, or trying to become pregnant
- you are breastfeeding your child
- you have myasthenia gravis (a chronic autoimmune neuromuscular disease which causes muscle weakness)
- you have stomach problems affecting passage and digestion of food
- you have or have had abnormal increases in heart rate or ischemic heart disease (e.g. angina)
- you have severe liver problems
- you have severe kidney problems
- you have problems emptying your bladder or if you have weak urine stream
- you are receiving treatment for an eye problem called narrow- angle glaucoma

APO-FESOTERODINE can cause angioedema (swelling of face or tongue, difficulty breathing) and anaphylactic reactions (hives, difficulty breathing, abdominal cramps, rapid heartbeat and feeling faint). If you experience any of these symptoms, stop taking APO-FESOTERODINE and see you doctor immediately.

APO-FESOTERODINE should not be given to patients under 18 years of age.

Do not drive a car or operate any machinery until you know how APO-FESOTERODINE affects you.

INTERACTIONS WITH THIS MEDICATION

The following list includes some, but not all, of the drugs that may increase the risk of side effects while receiving **APO-FESOTERODINE**. You should check with your doctor or pharmacist before taking any other medication with **APO-FESOTERODINE.**

Drugs that may interact with APO-FESOTERODINE include:

- other drugs that possess antimuscarinic/anticholinergic properties (drugs that cause blurred vision, constipation, dry mouth, etc.)
- antifungals (drugs to treat fungal infections, such as, fluconazole, ketoconazole, miconazole or itraconazole)
- antibiotics (ie. erythromycin, clarithromycin)
- vinblastine (a drug to treat some types of cancer)
- antidepressants (mood disorder drugs)
- antipsychotics (drugs to stabilize thinking and behavior)
- medications bought without a prescription or natural health product.

PROPER USE OF THIS MEDICATION

REMEMBER: This medication is for YOU. Never give it to others. It may harm them even if their symptoms are the same as yours.

Usual Dose: The usual starting dose is 4 mg once daily.

Take **APO-FESOTERODINE** with liquid and swallow the tablet whole. You can take **APO-FESOTERODINE** with or without food. Based upon your response and tolerability, your doctor may increase your dose to 8 mg once daily. The maximum dose for **APO-FESOTERODINE** is 8 mg once daily.

Your doctor may give you the lower 4 mg dose of **APO-FESOTERODINE** if you have certain medical conditions, such as severe kidney problems.

Take **APO-FESOTERODINE** as instructed by your doctor. Do not increase, decrease or stop taking **APO-FESOTERODINE** without first talking to your doctor.

Overdose:

If you think you have taken too much **APO-FESOTERODINE**, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss taking your tablet, take it as soon as you remember. But if it is almost time for the next dose, skip the missed dose and just take the next dose. Do not take more than one dose at a time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with most drugs, **APO-FESOTERODINE** can cause some side effects.

A very common side effect is dry mouth. Common side effects are constipation, urinary tract infection, dry eyes, upset stomach, dry throat, nausea, upper respiratory tract infection, painful urination, difficulty emptying your bladder, swelling of the extremities, and skin rash. Uncommon side effects are cough, back pain, abdominal pain, and insomnia. Other side effects that have been reported after the drug was marketed include: blurred vision, dizziness, headache, heart palpitations, angioedema, hypersensitivity reactions, hives, and itching.

If you experience dry mouth after taking **APO-FESOTERODINE**, there are a few ways that might help relieve the symptoms:

- Carry a bottle of water and sip a little bit throughout the day or suck on ice chips to provide moisture
- Chew sugarless gum or suck on sugarless hard candy to stimulate saliva production
- Avoid eating salty or spicy foods
- Avoid drinking carbonated, caffeinated and alcoholic beverages
- Avoid using mouth rinses that contain alcohol, as they may dry out the mouth
- Use a humidifier at night
- Ask your pharmacist to recommend an over-the-counter saliva substitute or oral lubricant

Check with your doctor or pharmacist right away if you have ***any*** bothersome or unusual effects while taking **APO-FESOTERODINE**.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	Severe Allergic reaction (hives, severe itching, difficulty breathing,			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
	abdominal cramps, rapid heartbeat and feeling faint)			
Uncommon	Acute Urinary Retention (inability to empty your bladder)			√
Uncommon	Angioedema (swelling of face or tongue, difficulty breathing)			√

This is not a complete list of side effects. For any unexpected effects while taking APO-FESOTERODINE, stop taking the drug and contact your doctor or pharmacist.

HOW TO STORE IT

Store between 15°C to 25°C. Protect from light and moisture.

You should not use your medication after the expiration date printed on the label.

Keep all medications out of the reach and sight of children. This medication could harm them.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about APO-FESOTERODINE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp). Find the Consumer Information on the manufacturer's website (http://www.apotex.ca/products) or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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