

## Pharmacotherapy Update on the Treatment of Overactive Bladder Syndrome: Focus on Fesoterodine

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**Abstract:** Overactive bladder is a highly prevalent condition that affects both males and females. The risk of developing overactive bladder increases with aging. There appear to be multiple etiologies for overactive bladder. Antimuscarinic agents have been the mainstay for pharmacologic treatment of overactive bladder. Their role is thought to be via antagonism with acetylcholine at the M3 receptor in the detrusor. More recently, the urothelium and suburothelium have been demonstrated to have muscarinic receptors and thus antimuscarinic agents may affect the afferent pathway component of overactive bladder symptoms. Historically, although effective, the use of antimuscarinic agents has been limited by poor tolerability. The development of once daily formulations and alternative methods of delivery, multiple dose agents and agents with variable muscarinic receptor affinity profiles has resulted in improved tolerability profiles while maintaining efficacy. Although effective, antimuscarinic agents typically improve OAB symptoms and are less likely to lead to complete resolution of symptoms. The success rates of antimuscarinic therapy are improved when used in combination with behavioral therapy. Fesoterodine is one of the most recent OAB agents to be approved by the FDA. It acts as a prodrug and is rapidly and extensively metabolized to 5-hydroxymethyltolterodine, which is also the active metabolite of tolterodine. Fesoterodine is available in two formulations and clinical studies have demonstrated a dose-related response in efficacy with fesoterodine. Fesoterodine is well tolerated, the most common side effects being those of dry mouth and constipation. There were very few discontinuations in the clinical trials due to either dry mouth or constipation. Fesoterodine's long-term efficacy and tolerability has been demonstrated in the 3-year open label extension trial with fesoterodine. A thorough QT study confirmed the absence of an effect on the QT interval with standard dosing of fesoterodine, 4 mg or a high dose, 28 mg of fesoterodine. Due to multiple metabolic pathways, via the CYP P450 system and excretion by the kidneys, there are limited dosing restrictions with fesoterodine. Fesoterodine is the only antimuscarinic therapy available that comes with the YOURWAY plan, a multidimensional program that brings together pharmacotherapy with education and skills training.

**Keywords:** fesoterodine, overactive bladder, antimuscarinic, urgency

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## Introduction

Overactive bladder is a common condition, with prevalence rates in the United States and Europe reported to be 12% to 17%.<sup>1-3</sup> Overactive bladder (OAB) affects males and females and the prevalence increases with age.<sup>1,2</sup> OAB is defined by the International Continence Society as urgency with or without urgency urinary incontinence (UUI) usually with frequency and nocturia.<sup>4</sup> There are several proposed etiologies for OAB including neurogenic, myogenic and a combination of the two. OAB has a significant impact on quality of life<sup>5-7</sup> as well as associated medical co-morbidities, such as increased incidence of urinary tract infections, skin irritation/infection, and increased risk of falls and fractures in older females with OAB and incontinence as well as a strong correlation with depression.<sup>8-12</sup> Despite its significant impact, both medically and financially, overactive bladder remains under-diagnosed and under-treated. Currently, first line therapies for overactive bladder consist of pharmacologic therapy and/or behavioral therapy. Several antimuscarinic agents are approved by the FDA for treatment of overactive bladder. These agents have been shown to improve OAB symptoms as well as improve quality of life. Although they are all similar in their mechanism of action, differences exist in their method of administration, chemical structure, muscarinic receptor affinity, metabolism, dose flexibility and side effect and safety profile. Fesoterodine (Toviaz, Pfizer) is one of the newer antimuscarinics approved by the FDA for the treatment of OAB. It is a unique, once daily formulation that is available in two doses.

## Pharmacodynamics of fesoterodine

### Mechanism of action

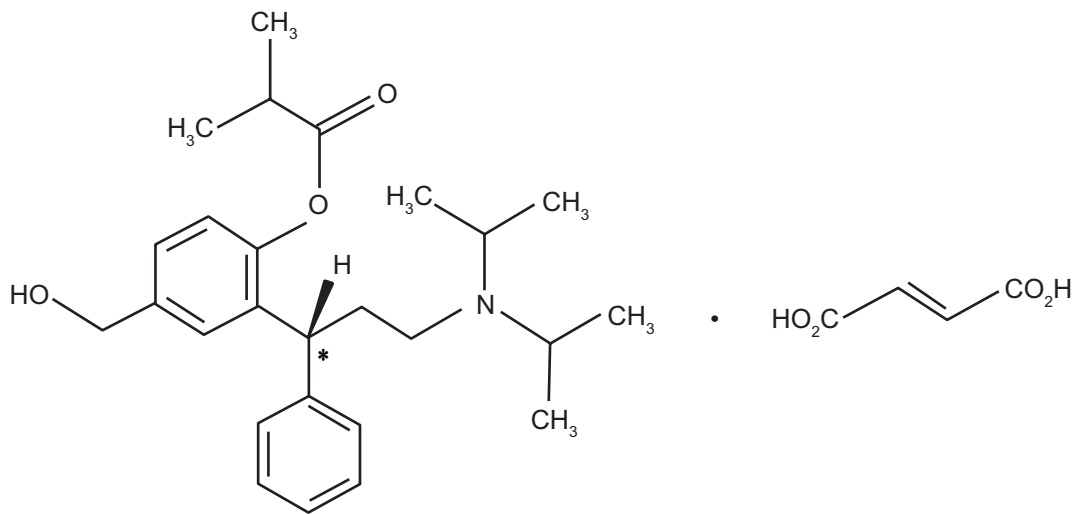
Fesoterodine is a competitive muscarinic receptor antagonist. The parent molecule itself, fesoterodine fumarate, is not a potent muscarinic receptor antagonist, rather it is the active metabolite, 5-hydroxymethyltolterodine, which is responsible for the antimuscarinic activity of fesoterodine.<sup>13</sup> After oral administration, fesoterodine is rapidly and extensively hydrolyzed by nonspecific ubiquitous esterases to 5-hydroxymethyltolterodine.<sup>14</sup> 5-hydroxymethyltolterodine (5-HMT) is a balanced muscarinic receptor blocker without selectivity for any particular muscarinic receptor subtype.<sup>15</sup> There are 5 different muscarinic receptors

in the body, two of which are located in the bladder, M2 and M3.<sup>16</sup> Muscarinic receptors are located in the detrusor muscle of the bladder as well as the urothelium/suburothelium. The role of muscarinic receptors in the detrusor is more clearly defined than those in the urothelium/suburothelium.<sup>17</sup> Although the M2 receptor is more abundant in the detrusor, it is the M3 receptor that has been established to play a key role in detrusor contractility. When stimulated M3 receptors directly evoke bladder smooth muscle contraction. Antimuscarinic agents bind competitively to the muscarinic receptor, preventing the binding of acetylcholine and subsequent stimulation of a detrusor contraction. M2 receptors appear to indirectly reverse sympathetically mediated smooth muscle relaxation. Inhibition of these muscarinic receptors in the bladder is presumed to be the mechanism by which fesoterodine produces its effects. In an 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.<sup>18</sup> These findings are consistent with an antimuscarinic effect on the bladder. The significance of muscarinic receptor selectivity on efficacy measures in OAB is not fully understood.

It is postulated that muscarinic receptors in the urothelium and suburothelium may play a role in afferent pathway-mediated overactive bladder symptoms, however, further studies are needed to determine the role of these receptors and the impact of their antagonism.

## Chemistry

Fesoterodine was developed with the goal of providing a chemical which was rapidly and extensively metabolized to the active metabolite, 5-HMT. This is accomplished by the rapid hydrolysis by ubiquitous, non-specific esterases. This conversion is so rapid and extensive, that fesoterodine cannot be detected in the plasma after oral administration.<sup>18,19</sup> Fesoterodine fumarate is designated as isobutyric acid 2-(R-3-diisopropylammonium-1-phenylpropyl)-4-(hydroxymethyl) phenyl ester hydrogen fumarate (Fig. 1). The empirical formula is  $C_{30}H_{41}NO_7$  and its molecular weight is 527.66.<sup>18</sup>



The asterisk (\*) indicates the chiral carbon.

**Figure 1.** Chemical structure of Fesoterodine (Prescribing information, Toviaz).

## Metabolism and Pharmacokinetics

### Receptor binding and activity

Fesoterodine's affinity for the M2 and M3 muscarinic receptors is 2 to 3 orders of magnitude (i.e. 100- to 500-fold) weaker than that of 5-HMT. This significantly lower activity of fesoterodine, combined with the fact that fesoterodine is not detectable after oral dosing due to rapid conversion to 5-HMT, indicates that fesoterodine functions as a pro-drug, and that 5-HMT alone is responsible for the antimuscarinic activity in patients treated with fesoterodine. 5-HMT is a balanced antimuscarinic agent, with respect to affinity for the M2 and M3 receptors. The  $K_i$  (nM) for M2 is 2.0 and for M3 2.5 and for M1 2.3, M4 2.8, M5 2.9.<sup>20</sup>

### Absorption and distribution

Fesoterodine is available as an extended release tablet in two doses, 4 mg and 8 mg. A matrix platform is used for extended delivery of once-daily fesoterodine. Upon ingestion, the polymer swells to form a gel layer. Fesoterodine diffuses from the core and the tablet erodes over the course of the day. Thus the tablets cannot be chewed, divided or crushed as this would increase the surface area of the tablet and thus unpredictably affect the release rate.<sup>18</sup>

After oral administration, fesoterodine is well absorbed. Due to rapid and extensive hydrolysis by nonspecific esterases to its active metabolite, 5-HMT, fesoterodine cannot be detected in plasma.<sup>21</sup>

The bioavailability of 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 were proportional to the dose. Maximum plasma levels are reached after approximately 5 hours. No accumulation occurs after multiple-dose administration. The time to maximum plasma concentration ( $t_{max}$ ) is roughly 5 hours for both the 4 mg and 8 mg doses of fesoterodine. The range varies from 2–6 hours in extensive CYP2D6 metabolizers to 5–6 hours in poor CYP2D6 metabolizers.<sup>18,19,21</sup> Up to 10% of white people and up to 19% of black people have been shown to lack CYP2D6 isozyme activity and thus are classified as poor CYP2D6 poor metabolizers.<sup>23</sup> The remainder of the population are extensive metabolizers.  $C_{max}$  and AUC (area under the curve) of the active metabolite are increased 1.7- and 2-fold, respectively, in CYP2D6 poor metabolizers as compared to extensive metabolizers.<sup>18,19,21</sup>

### Metabolism and elimination

After oral administration, fesoterodine fumarate is rapidly and extensively metabolized by ubiquitous esterases to 5-HMT. Both hepatic metabolism and renal excretion contribute significantly to the elimination of 5-HMT.<sup>21</sup>

In the liver 5-HMT is metabolized by two major pathways involving CYP2D6 and CYP3A4 to carboxy, carboxy-N-desisopropyl and N-desisopropyl



metabolites. These metabolites do not contribute significantly to the antimuscarinic activity of fesoterodine.<sup>19,21</sup> After oral administration of fesoterodine, approximately 70% of the administered dose is recovered in the urine as 5-HMT (16%), carboxy metabolite (34%), carboxy-N-desisopropyl metabolite (18%), or N-desisopropyl metabolite (1%), and a smaller amount (7%) is recovered in the feces.<sup>18</sup> The apparent terminal half-life after oral administration is about 7 hours.<sup>16,18</sup>

### Pharmacokinetics in special populations

There is no dosage adjustment recommended for age, gender or race. Subject demographics, such as age, gender and race, do not have a clinically meaningful effect on 5-HMT pharmacokinetics or pharmacodynamics.<sup>22</sup> The pharmacokinetics of fesoterodine have not been studied in pediatric patients.<sup>18</sup>

In the Phase 2 and 3, placebo-controlled, efficacy and safety studies, 515 (33%) of the 1567 patients who received fesoterodine 4 mg/day or 8 mg/day were 65 years of age and older, and 140 (9%) were 75 years of age or older. There were no overall differences in safety or effectiveness observed between patients younger than 65 years of age and those 65 years of age and older in these studies. Those patients 75 years of age and older did experience a higher incidence of antimuscarinic adverse events, including dry mouth, constipation, dyspepsia, increased post-void residual urine, dizziness (on 8 mg dose only) and urinary tract infection. No dose adjustment is recommended for the elderly. The pharmacokinetics of fesoterodine are not significantly influenced by age.<sup>18</sup>

There do not appear to be any differences in the pharmacokinetics of fesoterodine between Caucasian and Black healthy subjects even though there are differences in the prevalence of CYP2D6 poor metabolizers between Caucasians and African Americans as previously noted.<sup>23</sup>

### Renal insufficiency

The effects of renal impairment on the pharmacokinetics of a single 4 mg oral dose of fesoterodine were assessed in 8 healthy subjects and 8 subjects each with mild, moderate, or severe renal impairment. When compared to results in healthy subjects, the maximum plasma concentration of 5-HMT was increased by 1.4-, 1.5- and 2.0-fold and the area

under the curve (AUC) increased by 1.6-, 1.8- and 2.3-fold in subjects with mild, moderate, and severe renal impairment, respectively. The median time of observed maximal drug concentration (5–6 hours) and mean terminal half-life (6–7 hours) of 5-HMT was unaffected by renal function. The unbound fraction of 5-HMT in the plasma (0.43–0.54) was comparable across all groups. Based on this information, no dosage adjustment is recommended in patients with mild or moderate renal insufficiency (CL<sub>cr</sub> ranging from 30–80 mL/min). The maximum recommended dose is 4 mg in patients with severe renal insufficiency (CL<sub>cr</sub> < 30 mL/min).<sup>16,24</sup>

### Hepatic impairment

No dosage adjustment is recommended in patients with mild or moderate hepatic impairment. In patients with moderate (Child-Pugh B) hepatic impairment, C<sub>max</sub> and AUC of the active metabolite are increased 1.4- and 2.1-fold, respectively, as compared to healthy subjects.<sup>25</sup> Fesoterodine has not been studied in patients with severe hepatic impairment (Child-Pugh C) and therefore fesoterodine is not recommended for use in these patients.

### Differences in Pregnancy/Nursing mothers

Fesoterodine is pregnancy category C. There are no adequate and well-controlled studies using fesoterodine in pregnant women. Therefore, fesoterodine should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. It is not known whether fesoterodine is excreted in human milk. Thus, fesoterodine should be used during nursing only when the potential benefit outweighs the potential risk for the neonate/infant.

## Drug–Drug Interactions

### Drugs metabolized by the cytochrome P450 System

At therapeutic concentrations, the active metabolite of fesoterodine, 5-HMT, does not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E, or 3A4 nor does it induce CYP1A2, 2B6, 2C9, 2C19, or 3A4 *in vitro*.<sup>18</sup>

### CYP3A4 inhibitors

An open-label, two-way, randomized, crossover study was performed to assess the effects of co-administration of ketoconazole and fesoterodine on the PK, safety and tolerability of fesoterodine.



The study was divided into two treatment periods. In the first period of the study patients received a single oral dose of fesoterodine 8 mg on day 2. During the second period of the study, patients received ketoconazole 200 mg orally twice a day on days -4 to -1. On Day 1, a single dose of fesoterodine 8 mg was given with ketoconazole 200 mg, followed by a second 200 mg dose of ketoconazole twelve hours later. On Day 2, ketoconazole 200 mg was given twice daily. The two treatment periods were completed by subjects in a randomized order, and the treatment periods were separated by a washout period of at least 2 weeks. Eighteen men were enrolled and randomized in the study, 12 were CYP2D6 extensive metabolizers (EMs) and 6 were CYP2D6 poor metabolizers (PMs). Nine males in the fesoterodine group and eight in the fesoterodine plus ketoconazole group completed dosing. The exposure of 5-HMT (expressed as AUC and C<sub>max</sub>) was approximately two-fold higher in PMs than in the EMs, both after fesoterodine alone and after concomitant ketoconazole administration. Compared to fesoterodine alone, concomitant administration of ketoconazole resulted in an increase in AUC of 5-HMT by a factor of 2.3 and 2.5 and an increase in C<sub>max</sub> by a factor of 2.0 and 2.1 in EMs and PMs, respectively. In EMs, the t<sub>1/2</sub> ranged from 7 hr for fesoterodine alone to 7.7 hrs during concomitant ketoconazole. In contrast, with PMs, the t<sub>1/2</sub> ranged from 7.0 hrs for fesoterodine alone to 8.4 hrs with concomitant ketoconazole.<sup>26</sup>

### CYP3A4 Inducers

An open-label, sequential study to the aforementioned CYP3A4 inhibitor study was performed to evaluate the effects of the co-administration of rifampicin on the PK, safety, and tolerability of fesoterodine. This study also had 2 treatment periods. In the first treatment period, individuals received a single dose of fesoterodine 8 mg on day 1. In the second treatment period, rifampicin 600 mg once daily was administered in the evening on days 3–8. On day 9, a single oral dose of fesoterodine was given in the morning followed by oral administration of rifampicin in the evening. On day 10, rifampicin was administered orally in the evening. For both EMs and PMs, exposure of 5-HMT decreased during concomitant administration of fesoterodine and rifampicin compared to fesoterodine alone. The mean AUC was decreased by

a factor of 4.4 and 4.6 and C<sub>max</sub> was decreased by a factor of 3.6 and 3.6 in EMs and PMs.<sup>26</sup>

### CYP2D6 inhibitors

The interaction with CYP2D6 inhibitors was not tested clinically. In poor metabolizers for CYP2D6, representing a maximum CYP2D6 inhibition, C<sub>max</sub> and AUC of 5-HMT, the active metabolite are increased, 1.7- and 2-fold, respectively.<sup>27</sup>

### Effects of fesoterodine on the suppression of ovulation by oral contraception

Thirty women were enrolled in a trial to evaluate the effects of fesoterodine 8 mg versus placebo once daily on oral contraceptive pharmacokinetics and on pharmacodynamic effects on progesterone, luteinizing hormone, follicle-stimulating hormone, and estradiol plasma levels. Fesoterodine did not influence the suppression of ovulation by oral hormonal contraception. LH, FSH and ethinylestradiol levels were sufficiently suppressed to suggest absence of ovulation during concomitant administration of fesoterodine. The mean plasma concentration-time profiles for ethinylestradiol and levonorgestrel were similar both in the absence and presence of fesoterodine.<sup>26</sup>

### Therapeutic use

Fesoterodine fumarate extended release is approved for the treatment of OAB with the symptoms of urgency urinary incontinence, urgency, and frequency.

Multiple studies have demonstrated the clinical efficacy of fesoterodine fumarate for the treatment of OAB.

### Dosing

Fesoterodine fumarate is available as once daily formulation, in two doses, 4 mg and 8 mg. The recommended starting dose of fesoterodine is 4 mg once daily. Based on individual response and tolerability, the dose may be increased to 8 mg once day. Fesoterodine should be taken with liquid and swallowed whole. Fesoterodine can be administered with or without food, and should not be chewed, divided, or crushed.<sup>16</sup>

### Clinical efficacy

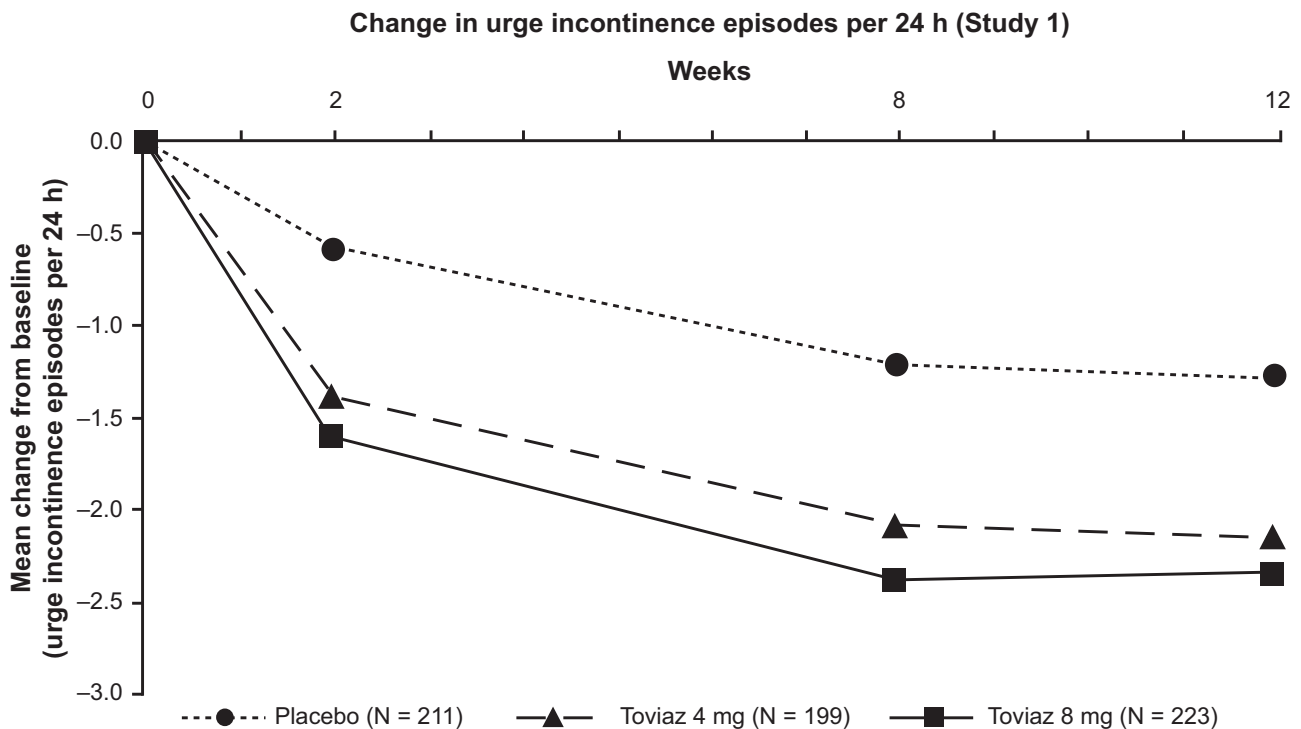
The clinical efficacy of fesoterodine was evaluated in two, Phase 3, randomized, double-blind, placebo-controlled, 12-week studies for the treatment of

OAB with symptoms of UUI, urgency, and urinary frequency.<sup>28,29</sup> Patients were randomized to a fixed dose of fesoterodine 4 mg or 8 mg/day or placebo. In one of the studies, the non-US study, study 2,290 patients were randomized to an active control arm (an oral antimuscarinic agent).<sup>28</sup> For the combined studies, a total of 554 patients received placebo, 554 patients received fesoterodine 4 mg/day and 566 patients received fesoterodine 8 mg/day. The primary efficacy endpoints were the mean change in the number of UUI episodes per 24 hours and the mean change in the number of micturitions (frequency) per 24 hours. The mean change in the voided volume per micturition was a secondary endpoint.<sup>28,29</sup>

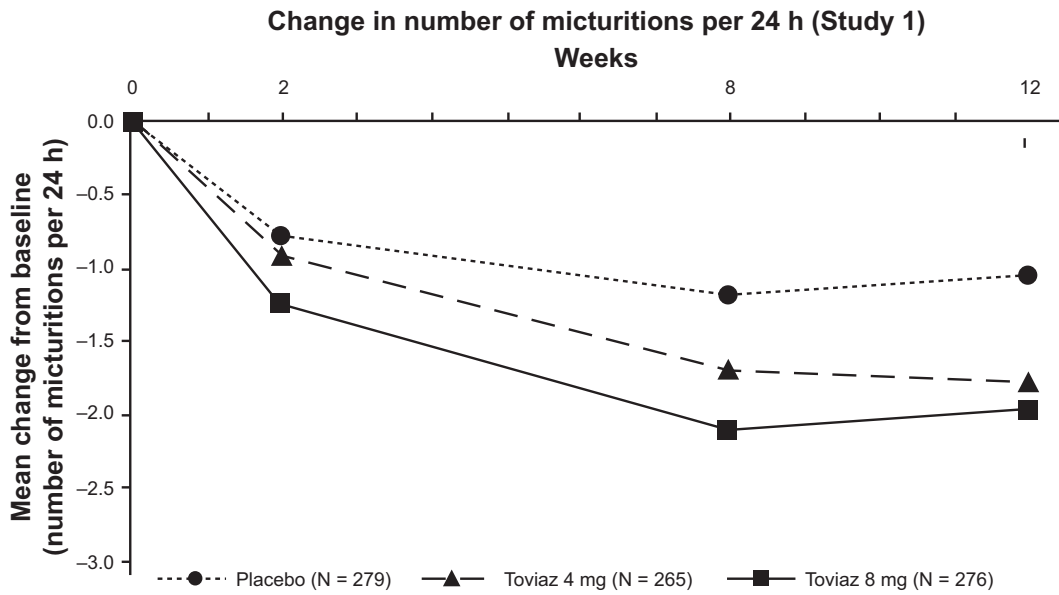
In study 1 (US study) the mean number of UUI episodes changed from a baseline of 3.8 to 1.74 (−2.06) for fesoterodine 4 mg/day which was statistically significant when compared to placebo, similarly with 8 mg/day of fesoterodine a statistically significant decrease was also noted (baseline 3.7, to 1.43, −2.27). (Fig. 2) With respect to micturition frequency, significant decreases were noted for both 4 mg and 8 mg of fesoterodine when compared to placebo. Baseline mean numbers of micturitions were 11.6 and 11.9 for the 4 mg and 8 mg doses, respectively and a mean

reduction of 1.74 micturitions per 24 hours and 1.94 micturitions per 24 hours was noted for the 4 mg and 8 mg groups, respectively. (Fig. 3) Mean volume voided increased significantly compared to placebo with both treatment groups. The mean increase from baseline for the 4 mg group was 27 ml and 33 ml for the 8 mg group.<sup>29</sup>

In study 2 (non-US study), similar changes were noted, a decrease from a mean baseline of 3.9 UUI episodes to 2.13 (−1.77) with 4 mg fesoterodine and with 8 mg of fesoterodine a decrease from baseline of 3.9 urge incontinence episodes per 24 hrs to a mean of 1.48 urge incontinence episodes per 24 hrs (−2.42). (Fig. 4) When compared to placebo, a statistically significant decrease from baseline for number of micturitions per 24 hours was noted with the 8 mg group only. A mean decrease of 1.86 micturitions per 24 hours (p value compared to placebo = 0.032) was noted for the 4 mg group and a mean decrease of 1.94 micturitions per 24 hours (p value compared to placebo < 0.001) for the 8 mg group. (Fig. 5) Lastly, a significant increase in mean volume voided compared to placebo was noted with the 8 mg group. A mean increase in volume voided of 17 ml (p value compared to placebo of 0.150) for the 4 mg group and



**Figure 2.** Change in urge incontinence episodes per 24 hours with fesoterodine 4 mg and 8 mg compared to placebo in U.S. Study (Prescribing information, Toviaz).



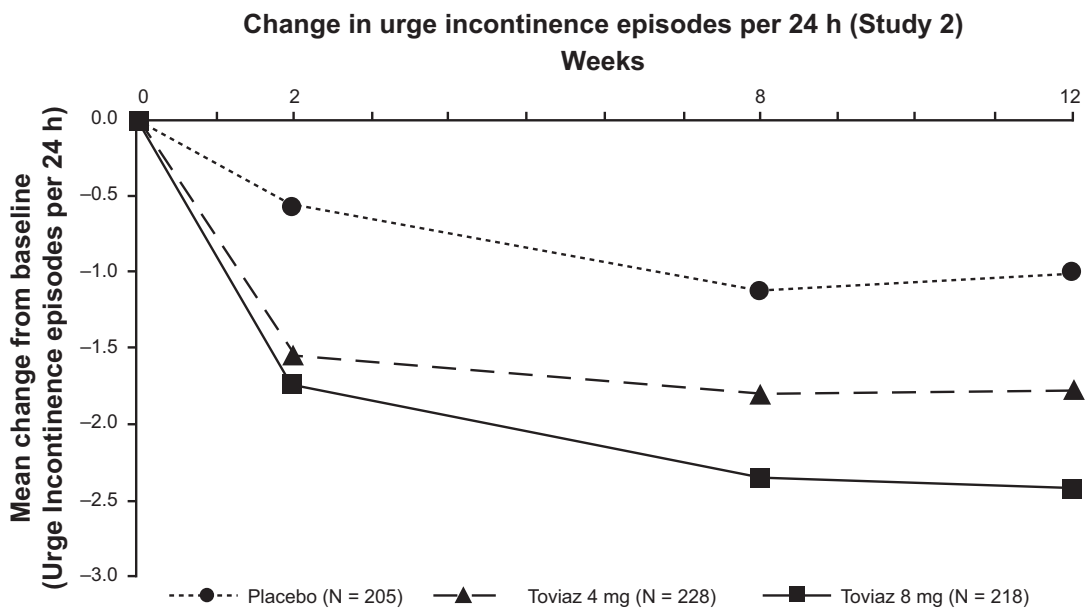
**Figure 3.** Change in number of micturitions per 24 hours with fesoterodine 4 mg and 8 mg compared to placebo in U.S. Study (Prescribing information, Toviaz).

33 ml (p value compared to placebo of < 0.001) for the 8 mg group.<sup>28</sup>

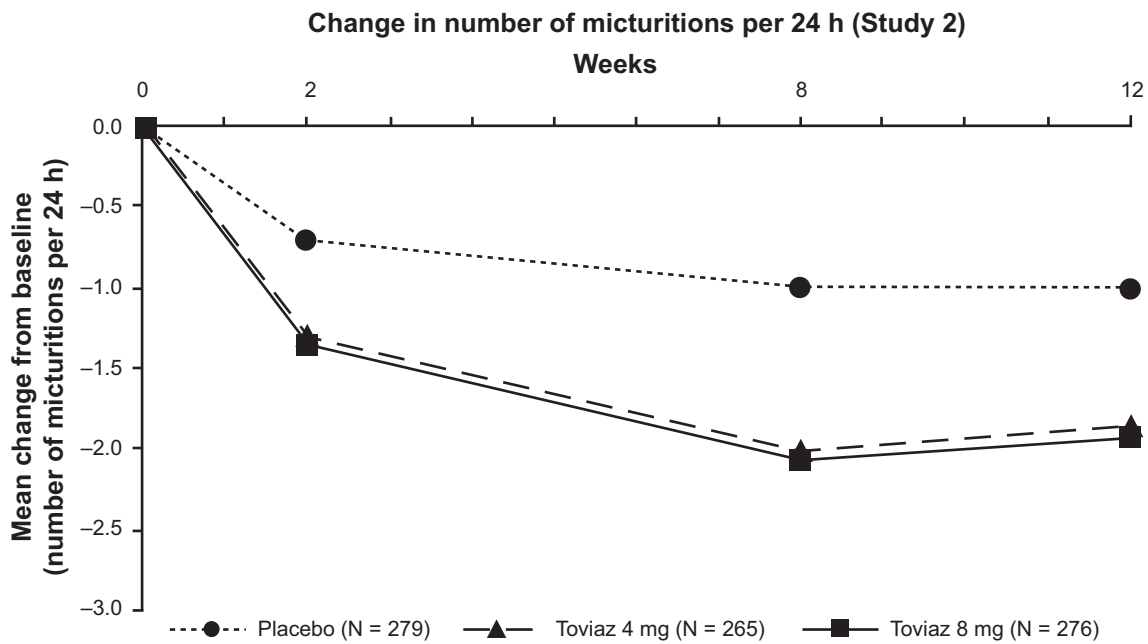
Dose response curves demonstrated separation from placebo as early as 2 weeks for all of the efficacy parameters, with continued improvement in response out to at least 8 weeks, and for some parameters, 12 weeks.<sup>28,29</sup>

A post hoc analysis of pooled data from the two Phase III clinical trials evaluating the efficacy and

tolerability of fesoterodine in female patients demonstrated that by weeks 2 and 12, significant improvements in all five bladder diary variables were seen with both 4 mg and 8 mg of fesoterodine compared to placebo. In addition, fesoterodine 8 mg was significantly more efficacious than fesoterodine 4 mg in improving UII episodes and continent days per week in the study group of women only.<sup>30</sup>



**Figure 4.** Change in urge incontinence episodes per 24 hours with fesoterodine 4 mg and 8 mg compared to placebo in European Study (Prescribing information, Toviaz).



**Figure 5.** Change in number of micturitions per 24 hours with fesoterodine 4 mg and 8 mg compared to placebo in European Study (Prescribing information, Toviaz).

### Dose flexibility

The effects of flexible-dose fesoterodine on OAB symptoms and treatment satisfaction were evaluated in a 12-week, open-label, flexible-dose study of adults with OAB ( $\geq 8$  micturitions and  $\geq 3$  urgency episodes per 24 hours) who had been treated with prior tolterodine (immediate release or extended release) for OAB within 2 years of screening and who had reported dissatisfaction with tolterodine treatment. Individuals were started on fesoterodine 4 mg once daily and after 4 weeks they were allowed to increase to 8 mg once daily based on the subject's and physician's subjective assessment of efficacy and tolerability. Individual's completed 5-day diaries, the patient perception of bladder condition (PPBC) and the OAB questionnaire (OAB-q) at baseline and week 12 and rated treatment satisfaction at week 12 using the Treatment Satisfaction Questionnaire (TSQ). Of the 516 patients treated, approximately 50% chose to increase to 8 mg at 4 weeks. Significant improvements from baseline to week 12 were noted in micturition frequency, UUI episodes, micturition-related urgency episodes and severe micturition-related urgency episodes per 24 hrs (all  $p < 0.0001$ ). Approximately 80% of individuals who completed the TSQ at week 12 reported satisfaction with treatment, 38% reported being very satisfied. Using the

PPBC, 83% of individuals reported improvement at week 12 with 59% reporting improvement  $\geq 2$  points. Significant improvements ( $p < 0.0001$ ) from baseline were noted in OAB-q symptom bother and HRQL.<sup>31</sup>

A pooled post hoc analysis of the two phase 3 trials showed that fesoterodine 8 mg was significantly more efficacious than fesoterodine 4 mg in improving UUI episodes, mean volume voided per micturition, continent days per week (extrapolated from 3-day diaries), and subject-reported Treatment Response at week 12, indicating an apparent efficacy dose-response effect on these end points.<sup>32</sup>

### Impact on quality of life

Pooled data from the two aforementioned Phase III studies were analyzed to determine the effects of fesoterodine on quality of life.<sup>33</sup> For patients with OAB, the impairment of QOL and symptom bother are the drivers of treatment-seeking behavior.<sup>34,35</sup> A post hoc inferential analysis assessed treatment-related effects on health related quality of life (HRQoL) using the King's Health Questionnaire (KHQ), International Consultation on Incontinence Questionnaire—short form (ICIQ-SF), and a six-point Likert Scale used by patients to rate the severity of problems related to their bladder condition, and treatment response





(a yes/no variable defined from a four-point Treatment Benefit Scale).<sup>28,29,33</sup> Patients completed the KHQ, the ICIQ-SF, and the Likert scale at baseline and end of study.

The KHQ is a 33-item multidimensional disease-specific questionnaire for assessing men and women with LUTS.<sup>36</sup> The KHQ has nine domains: Role Limitations, Physical Limitations, Social Limitations, Personal Relationships, Emotions, Sleep/Energy, Severity/Coping, Incontinence Impact, and General Health Perception. The minimal importance difference (MID), the minimal improvement in HRQoL score that confers clinical benefit to the subject, have been established for the KHQ. Changes in KHQ domain scores  $\geq 5$  points from baseline are considered to be meaningful by the subject.<sup>37</sup> The minimal clinically important change in the number of UUI episodes is a reduction of more than 3 UUI episodes per week from baseline.<sup>38</sup> The ICIQ-SF is a questionnaire designed for evaluating patients with UI.<sup>39</sup> It has three scored items that assess urinary frequency, urinary leakage and perceived impact of these symptoms on subject's daily lives with scores ranging from 0 (low bother) to 21 (maximum bother).

HRQoL was significantly improved with fesoterodine 4 mg and 8 mg compared to placebo. In the end the fesoterodine 8 mg group had statistically significant improvements over placebo in eight of nine KHQ domains and fesoterodine 4 mg showed statistically significant improvements over placebo in seven of nine domains of the KHQ. Fesoterodine 8 mg gave better results than 4 mg in two domains, Emotions and Severity/Coping ( $p < 0.05$ ). All treatment groups reported significant improvement in the ICIQ-SF score vs. placebo ( $p < 0.001$ ). A major improvement in bladder condition (defined as a  $\geq 2$  point change on the Likert scale assessment bladder condition) was noted in 33% of patients on fesoterodine 4 mg and 38% of patients on fesoterodine 8 mg versus 21% on placebo ( $p < 0.001$ ). Lastly, the percentage of patients reporting a positive treatment response was significantly higher in those receiving fesoterodine than those receiving placebo. This improvement was seen at 2 weeks and maintained throughout the study. In addition, there were statistically significant differences between the doses in favor of fesoterodine 8 mg, both at 2 and 12 weeks.<sup>33</sup>

## Efficacy in pediatric and adolescent populations

The safety and effectiveness of fesoterodine fumarate in pediatric patients has not been established.

## Safety and tolerability

The safety of fesoterodine was evaluated in Phase 2 and 3 controlled trials in a total of 2859 patients, of which 2288 were treated with fesoterodine. Of the 2288 patients who received fesoterodine, 782 received fesoterodine 4 mg/day and 785 received fesoterodine 8 mg/day in Phase 2 or 3 studies with treatment periods of 8 or 12 weeks.<sup>18</sup>

A total of 1964 patients participated in two 12-week, Phase 3 efficacy and safety studies and subsequent open label extension studies. In the two Phase 3 studies combined, 554 patients received fesoterodine 4 mg/day whereas 556 received fesoterodine 8 mg/day.<sup>28,29</sup>

Overall, the incidence of serious adverse events was low, with the incidence of serious adverse events in patients receiving placebo, fesoterodine 4 mg and fesoterodine 8 mg reported to be 1.9%, 3.5% and 2.9%, respectively. Of these serious adverse events, only 4 patients receiving fesoterodine had a serious adverse event, angina, chest pain, gastroenteritis, and QT prolongation on ECG in each patient that may or was felt to be related to fesoterodine.<sup>18</sup>

The more commonly reported adverse events in patients treated with fesoterodine were dry mouth and constipation. (Table 1) Dry mouth was more frequently reported in the fesoterodine 8 mg/day group (35%) than in those taking 4 mg/day (19%), or placebo (7%). The majority of patients reporting dry mouth experienced mild to moderate dry mouth and  $<1\%$ ,  $<1\%$  and 3% of patients receiving placebo, fesoterodine 4 mg, and fesoterodine 8 mg, respectively, reported severe dry mouth. Discontinuation rates secondary to dry mouth were low, 0.4%, 0.4% and 0.8% in patients taking placebo, fesoterodine 4 mg, and fesoterodine 8 mg, respectively. Constipation was the second most commonly reported adverse event and was reported in 2% of individuals receiving placebo, 4% on fesoterodine 4 mg/day and 6% in those taking 8 mg/day. Discontinuation rates secondary to constipation were 0%, 0% and  $<1\%$  in patients taking placebo, fesoterodine 4 mg and fesoterodine 8 mg, respectively. Other less common adverse events reported in  $>2\%$  subjects treated with

**Table 1.** Incidence of Adverse Effects occurring more often than placebo and in  $\geq 1\%$  patients in phase III trials.

System organ class/Preferred term	Placebo N = 554%	Fesoterodine 4 mg/day N = 554%	Fesoterodine 8 mg/day N = 566%
<b>Gastrointestinal disorders</b>			
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
<b>Infections</b>			
Urinary tract infection	3.1	3.2	4.2
Upper respiratory tract infection	2.2	2.5	1.8
<b>Eye disorders</b>			
Dry eyes	0	1.4	3.7
<b>Renal and urinary disorders</b>			
Dysuria	0.7	1.3	1.6
Urinary retention	0.2	1.1	1.4
<b>Respiratory disorders</b>			
Cough	0.5	1.6	0.9
Dry throat	0.4	0.9	2.3
<b>General disorders</b>			
Edema peripheral	0.7	0.7	1.2
<b>Musculoskeletal disorders</b>			
Back pain	0.4	2.0	0.9
<b>Psychiatric disorders</b>			
Insomnia	0.5	1.3	0.4
<b>Investigations</b>			
ALT increased	0.9	0.5	1.2
GGT increased	0.4	0.4	1.2
<b>Skin disorders</b>			
Rash	0.5	0.7	1.1

Patients also received fesoterodine 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 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.

**Note:** This is taken from the fesoterodine (Toviz) prescribing information.

**Abbreviations:** ALT, alanine aminotransferase; GGT, gamma glutamyltransferase.

4 mg or 8 mg of fesoterodine included urinary tract infection, headache and dry eyes. Central nervous system adverse events with fesoterodine occurred at the same rate as placebo in both trials.<sup>18,28,29</sup>

Subjects completing the two 12-week, double-blind, Phase 3 trials were offered the opportunity to enroll in a 3 year open label extension study. The objective was to determine long-term safety and tolerability. All patients

(n = 890) started on 8 mg of fesoterodine and were allowed to reduce to 4 mg after 1 month and at later visits. At 1 month, only 16% of patients chose to decrease to 4 mg. Thereafter, at least 80% of continuing patients remained on 8 mg at every visit. Over the 3 years, 12.6% of patients discontinued due to adverse events, 1.7% due to dry mouth and 1.1% due to constipation. There were no unexpected adverse events.<sup>18</sup>



### Effects on QT interval

A thorough QT study was performed to investigate the effect of oral daily doses of fesoterodine 4 mg and 28 mg on the QT interval. The study was designed as a double-blind, randomized, placebo- and active-controlled, parallel-group study conducted over 3 days in 261 healthy volunteers aged 45–65 yrs, by day 3 subjects will have reached the steady state in drug exposure. QT intervals were evaluated with 12-lead Holter electrocardiography (ECG) over a 24-hour period at baseline (pretreatment), on day 1 and on day 3. Thirty-six ECGs were read per subject per day for a total of 108 ECGs per subject. On day 1 and day 3 changes from baseline in QT intervals with fesoterodine 4 mg and 28 mg were not different from what was observed in patients taking placebo. There was an increase in the QT interval with the active control moxifloxacin.<sup>16,18,40</sup>

### Place in therapy

There are multiple antimuscarinics currently available for use in the management of OAB. The majority of the agents are available in an oral single daily dose, although oxybutynin is available in a multiple times a day dosing formulation and a transdermal patch and gel formulation. Trospium chloride extended release is available in a single dose. Although tolterodine extended release is available in 2 doses, 2 mg and 4 mg, the standard recommended dose is 4 mg and the lower 2 mg dose is recommended only in special populations, such as those taking potent CYP3A4 inhibitors or those with severe renal impairment. The remaining agents solifenacin, darifenacin, oxybutynin extended release, and fesoterodine provide for dose flexibility. Efficacy of the various agents is generally thought to be similar and comparisons are limited by the lack of well designed comparative trials. The agents do vary in the incidence and types of adverse effects and their safety profiles. Fesoterodine is one of the most recent agents to be approved for the treatment of OAB. It is available in two once daily doses, 4 mg and 8 mg. Clinical trials have demonstrated dose-related improvements in voiding diary parameters, which has not been established with all of the other agents available in multiple doses. The tolerability of fesoterodine is well established. As with many of the other antimuscarinic agents, metabolism of the active metabolite of fesoterodine, 5-HMT is dependent on

the CYP 450 system and thus dosing modifications are recommended in select individuals. Unlike many of the other agents, the active metabolite, 5-HMT is also excreted unchanged in the urine. In addition to its proven efficacy and tolerability, fesoterodine comes with the YOURWAY plan, a multidimensional approach to OAB treatment that includes behavioral intervention.

### Improving compliance and outcomes

Use of antimuscarinics in the management of OAB has been limited by poor compliance. Often, individuals remain on pharmacologic therapy for as little as 3 months. Problems with persistence may be related to adverse effects, lack of adequate response to the drug, dietary/lifestyle behaviors which may exacerbate OAB symptoms and unrealistic expectations. Fesoterodine is the only agent that comes with a specialized, patient-friendly educational program designed to educate and empower patients to modify these factors, ideally to improve their overall treatment outcome. In addition to tips on dietary changes (such as decreasing/stopping caffeine and drinking an adequate amount of fluids), managing side effects and teaching healthy voiding habits, there is also information on behavioral techniques such as pelvic floor muscle exercises. This comprehensive program has been designed to allow patients to participate through a variety of medias including mail, telephone and computer-based contacts and is available to all patients taking fesoterodine.

### Disclosure

Pfizer: consultant, speaker, study investigator. Novartis: speaker, study investigator. Allergan: consultant

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