Efficacy and Tolerability of Fesoterodine in Men With Overactive Bladder: A Pooled Analysis of 2 Phase III Studies

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OBJECTIVES To assess the efficacy, safety, and tolerability of fesoterodine 4 and 8 mg in men with overactive bladder.

METHODS This was a subanalysis of pooled data from 358 men enrolled in 2 double-blind, placebo-controlled phase III trials. Subjects with frequency and urgency or urgency urinary incontinence (UUI) were randomized to fesoterodine 4 mg, fesoterodine 8 mg, or placebo for 12 weeks. Efficacy endpoints included bladder diary variables and subject-reported treatment response.

RESULTS By week 12, men treated with fesoterodine 4 or 8 mg had significantly greater median percentage improvements in micturition frequency, urgency episodes, and UUI episodes versus placebo and significantly greater percentages reported a treatment response versus placebo. Significant increases in mean voided volume (MVV) per micturition versus placebo occurred with fesoterodine 8 mg only. At week 12, fesoterodine 8 mg was significantly more efficacious than fesoterodine 4 mg in improving UUI episodes and MVV per micturition. The most commonly reported adverse events with fesoterodine 4 and 8 mg were dry mouth (12.5% and 37.7% vs 5.6% with placebo) and constipation (2.5% and 8.8% vs 0.8% with placebo). Symptoms suggestive of urinary retention were reported in 0.8%, 0.8%, and 5.3% of men in the placebo, fesoterodine 4 mg, and fesoterodine 8 mg groups, respectively; only 1 subject, in the fesoterodine 8 mg group, was catheterized.

CONCLUSIONS Fesoterodine 4 and 8 mg are generally safe, efficacious, and well tolerated for the treatment of overactive bladder symptoms in men. The 8 mg dose provides additional benefit and allows for treatment individualization. UROLOGY 75: 1149–1155, 2010. © 2010 Elsevier Inc.

Overactive bladder (OAB), defined as urgency with or without urgency incontinence and usually with increased daytime frequency and nocturia,[1] is widely believed to be associated with detrusor overactivity.[2] Approximately 11%-16% of men have OAB, as reported in population-based studies conducted in North America and Europe, and the prevalence increases with age.[3,4] Historically, lower urinary tract symptoms in older men, including OAB symptoms, have been presumed to result from benign prostatic enlargement or bladder outlet obstruction (BOO) and have been treated with agents that target the prostate or bladder outlet.[2] However, evidence suggests that lower urinary tract symptoms in men, including OAB symptoms, often occur independently from benign prostatic enlargement or BOO. For example, many men report OAB symptoms in the absence of voiding symptoms associated with benign prostatic enlargement,[3] and urodynamic studies have found that many men with storage symptoms or detrusor overactivity do not have BOO.[5,6] Further, men treated with drugs or surgery for prostatic enlargement may still experience persistent detrusor overactivity or OAB symptoms.[7,8]

Antimuscarinic agents are the mainstay of drug therapy for OAB. Antimuscarinics, either alone or in combination with an α-blocker, can significantly improve measures of OAB symptoms and health-related quality of

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life in men.[7,9-19] The use of antimuscarinics for OAB in men has been limited by concern over the possibility of precipitating acute urinary retention and increasing postvoid residual (PVR) urinary volume.[2] However, a number of 12-week placebo-controlled studies suggest that antimuscarinics are safe and well tolerated in men with OAB.[9,12,17-20]

Fesoterodine is a new nonselective antimuscarinic agent for the treatment of OAB.[21] After oral administration, fesoterodine is rapidly converted by ubiquitous esterases to the active metabolite, 5-hydroxymethyl tolterodine; the parent compound is not detectable in plasma, and all pharmacologic activity is attributable to 5-hydroxymethyl tolterodine.[21] In phase I studies, fesoterodine was shown to have a dose-dependent pharmacokinetic profile and low pharmacokinetic variability. In pivotal phase III trials, fesoterodine improved bladder diary variables and health-related quality of life measures in subjects with OAB,[22-24] with an apparent dose response on several diary and health-related quality of life outcomes.[24,25] The current subanalysis of pooled data from 2 phase III studies was conducted to assess the efficacy, safety, and tolerability of fesoterodine 4 and 8 mg vs placebo in men. The efficacy of the 8 mg dose vs 4 mg dose of fesoterodine was also compared, although the studies were not designed a priori to make this comparison. With a potential increase in the use of antimuscarinics in men, we believe that it is necessary to provide detailed information on the efficacy and safety of fesoterodine in men.

MATERIAL AND METHODS

This was a subanalysis of pooled data from 2 double-blind, placebo-controlled, fixed-dose, phase III trials, which had identical inclusion and exclusion criteria.[22,23] In both trials, eligible subjects were randomly assigned to treatment with fesoterodine 4 mg, fesoterodine 8 mg, or placebo, with doses taken each morning for 12 weeks. One of the trials[22] had a parallel active-control arm with tolterodine extended-release 4 mg; subjects in this arm were not included in the current analysis.

Subjects

Inclusion criteria for both studies were men or women aged ≥18 years with self-reported OAB symptoms for ≥6 months and urinary frequency (≥8 micturitions per 24 hours) and either urinary urgency (≥6 episodes) or urgency urinary incontinence (UUI; ≥3 episodes) documented in 3-day bladder diaries at baseline. Subjects had to report at least moderate bladder-related problems on a 6-point Likert scale. Key exclusion criteria were lower urinary tract pathology that could, in the opinion of the investigator, be responsible for urgency or incontinence; this included stress incontinence, urolithiasis, interstitial cystitis, urothelial tumors, and clinically relevant BOO as judged by the investigator (including PVR > 100 mL). Subjects who had symptomatic urinary tract infections; treatment within the past 2 weeks with antimuscarinic agents for OAB or any other medication indicated for treatment of OAB; treatment within the past 4 weeks with electrostimulation or bladder training; neurologic disease that could cause OAB; and those with clinically relevant arrhythmia, unstable angina, or a corrected QT interval (Bazett's formula) >500 millisecond were not included.[22,23] Only men were included in this pooled subanalysis.

Efficacy Assessments

Men recorded the time of each void, urgency episode, and UUI episode in a 3-day bladder diary completed before randomization and at 2 and 12 weeks after starting treatment. Subjects were instructed to consider urgency as "a sudden compelling desire to pass urine that is difficult to defer"[1] and to rate the degree of urgency for each episode, whether or not accompanied by voiding or incontinence, on a subjective 4-point scale: "no urgency," "mild urgency," "moderate urgency," or "severe urgency." Subjects were also given a urine cup and asked to record their voided volume in milliliters for each micturition on 1 of the 3 days in the bladder diary. In the primary analyses of the 2 phase III trials, the primary endpoint was the mean change from baseline to week 12 in number of micturitions per 24 hours. Coprimary endpoints were the mean change from baseline to week 12 in UUI episodes and the percentage of subjects reporting a treatment response at week 12 (treatment response was a yes/no variable derived from the validated 4-point Treatment Benefit scale[26]). Other efficacy variables assessed were median percentage change from baseline in number of micturitions, UUI episodes, and urgency episodes; mean change from baseline in urgency episodes; and mean voided volume (MVV) per micturition.

Safety and Tolerability Assessments

Safety and tolerability were evaluated on the basis of observation and assessment of adverse events. The seriousness, severity, and relatedness to treatment of adverse events were determined by the investigator at each visit. Postvoid residual volume was measured using ultrasound at screening; baseline; and weeks 2, 8, and 12; men who developed a PVR > 200 mL while receiving treatment were withdrawn from the trials. Urinary retention was defined as a PVR > 200 mL or based on the investigator's opinion that the subject had symptoms of retention, including urinary hesitation and decreased urine flow. Cardiovascular safety was monitored using electrocardiograms.

Statistical Analysis

Parametric analysis for continuous variables was performed for all randomized subjects for whom baseline and double-blind treatment data were obtained (full analysis set) using an analysis of covariance model with treatment and region as factors and baseline value as a covariate. Nonparametric sensitivity analysis was conducted using the Wilcoxon rank sum test. Treatment response was analyzed using the asymptotic normal approximation method. In exploratory analyses, median percentage change from baseline to weeks 2 and 12 was calculated for bladder diary endpoints, and statistical hypothesis testing was conducted. Safety analyses were conducted using data from all men who took ≥1 dose of study medication after randomization (safety population).

RESULTS

The safety population included 358 men (fesoterodine 4 mg, n = 120; fesoterodine 8 mg, n = 114; placebo, n = 124). Baseline demographic and clinical characteristics were statistically similar between treatment groups.

Most men were white (85.5%), with a mean age of 61 years, and 65.9% were incontinent at baseline. The mean time since first diagnosis or onset of OAB was approximately 8 years, with 23.2% of men having been diagnosed at least 10 years earlier. Overactive bladder symptoms also were statistically similar among the groups at baseline (Table 1).

Efficacy

At week 2 (first clinical evaluation after dosing), men treated with fesoterodine 4 mg had significantly greater median percentage improvement in UUI episodes vs placebo ($P = .0023$) (Fig. 1). In the fesoterodine 8-mg group, changes in all efficacy endpoints were significantly greater vs placebo at week 2, including median percentage and least squares (LS) mean improvements in number of micturitions ($P = .0017$, $P = .0001$, for median percentage and LS mean changes, respectively), urgency episodes ($P = .0156$, $P = .0004$), UUI episodes ($P < .0001$, $P = .0034$), and MVV per micturition ($P = .0015$, $P = .0036$); and percentage of subjects reporting a treatment response ($P = .005$) (Fig. 1, Table 1). Least squares mean improvements in micturition frequency and urgency episodes were significantly greater at week 2 with fesoterodine 8 mg compared with fesoterodine 4 mg ($P = .0099$, $P = .0367$ for frequency and urgency, respectively) (Table 1).

By week 12 (end of treatment), men treated with fesoterodine 4 mg had significantly greater median percentage and LS mean improvements from baseline in number of micturitions ($P = .017$, $P = .022$) and urgency episodes ($P = .004$, $P = .008$), as well as median percentage improvements in UUI episodes ($P = .023$) (Fig. 1, Table 1). Least squares mean improvements in UUI episodes and MVV were not significantly greater in men who received fesoterodine 4 mg compared with placebo (Table 1). Self-reported treatment response rates were significantly higher among men treated with fesoterodine 4 mg vs placebo at week 12 ($P = .009$) (Fig. 1). Men treated with fesoterodine 8 mg had statistically significant greater median percentage and LS mean improvements from baseline in number of micturitions, urgency episodes, and UUI episodes, as well as LS mean improvements in MVV, compared with placebo at week 12 ($P < .001$ for all) (Fig. 1, Table 1). Self-reported treatment response rates were significantly higher among men treated with fesoterodine 8 mg vs placebo at week 12 ($P < .001$) (Fig. 1).

Improvements by week 12 were significantly greater with fesoterodine 8 mg vs fesoterodine 4 mg for MVV ($P < .001$) (Table 1) and median percentage change in UUI episodes per 24 hours ($P = .035$) (Fig. 1).

Safety and Tolerability

The most common treatment-emergent adverse events (≥2% in any group) included dry mouth, constipation, and headache (Table 2). Most adverse events were of

Table 1. Bladder diary variables at baseline and change at weeks 2 and 12*

	Placebo			Fesoterodine 4 (mg)			Fesoterodine 8 (mg)		
	Baseline	Wk 2	Wk 12	Baseline	Wk 2	Wk 12	Baseline	Wk 2	Wk 12
Micturition frequency/24 h	12.3 (3.8) (n = 124)	−0.47 (0.23) (n = 123)	−0.79 (0.25) (n = 124)	12.3 (3.2) (n = 111)	−0.85 (0.25) (n = 106)	−1.59 (0.26)† (n = 111)	12.2 (4.0) (n = 109)	−1.74 (0.25)†,‡ (n = 105)	−2.13 (0.26)† (n = 109)
Urgency episodes/24 h	11.7 (3.7) (n = 124)	−0.50 (0.25) (n = 123)	−0.79 (0.29) (n = 124)	11.7 (3.7) (n = 111)	−1.00 (0.27) (n = 106)	−1.88 (0.30)† (n = 111)	11.7 (4.5) (n = 109)	−1.78 (0.27)†,‡ (n = 105)	−2.65 (0.31)† (n = 109)
UUI episodes/24 h§	3.4 (3.0) (n = 76)	−0.54 (0.29) (n = 75)	−1.13 (0.27) (n = 76)	3.2 (3.1) (n = 74)	−1.32 (0.29) (n = 72)	−1.79 (0.27) (n = 74)	3.1 (2.9) (n = 77)	−1.70 (0.28)† (n = 75)	−2.40 (0.26)† (n = 77)
MVV, mL	152 (n = 124)	−0.00 (8.49) (n = 122)	6.84 (6.18) (n = 123)	158 (n = 111)	15.04 (9.07) (n = 106)	7.74 (6.48) (n = 111)	152 (n = 109)	35.96 (9.11)† (n = 104)	39.91 (6.52)†,‡ (n = 108)

MVV = mean voided volume; UUI = urgency urinary incontinence.
* Baseline values are mean (standard deviation); wk 2 and 12 values are least squares mean (standard error of the mean).
† $P < .05$ vs placebo.
‡ $P < .05$ vs fesoterodine 4 mg.
§ Only men who reported ≥1 UUI episode at baseline were included in this analysis.

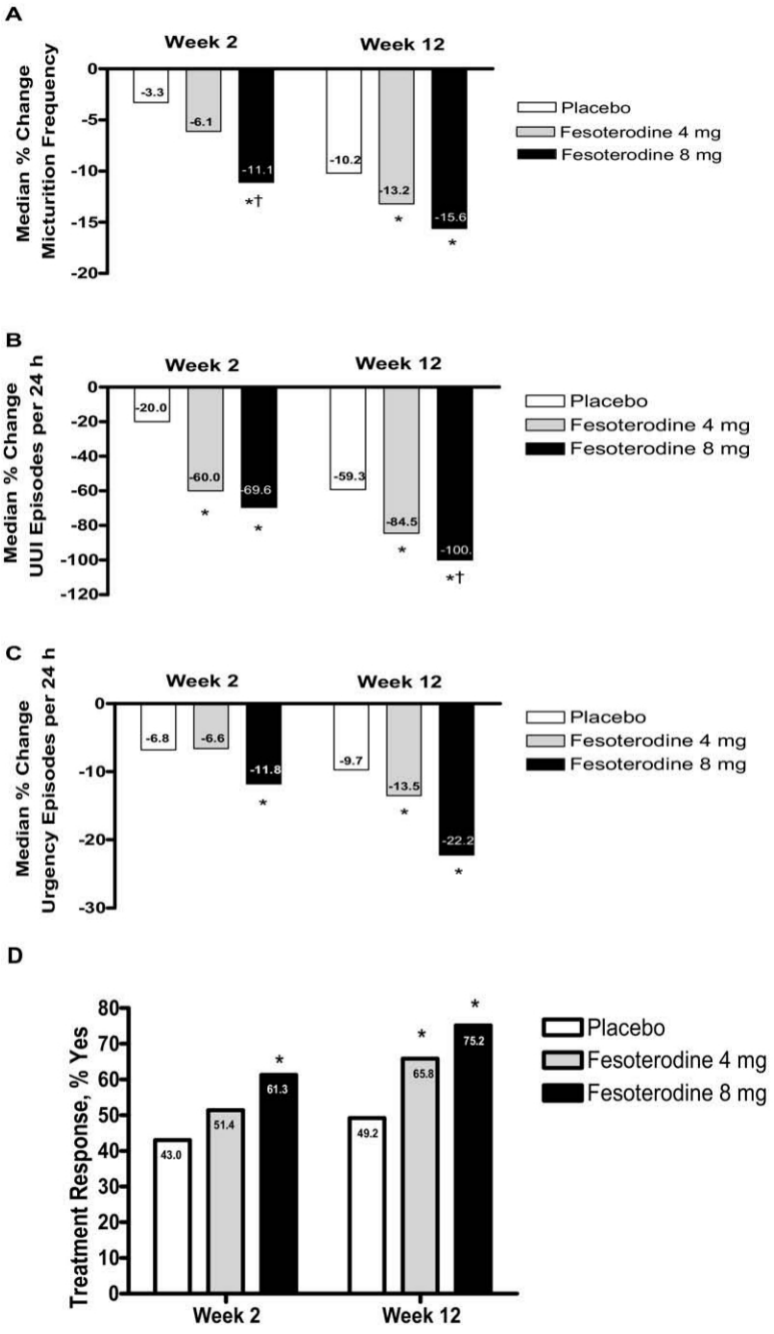

Figure 1. Median percentage change from baseline in **(A)** micturition frequency, **(B)** urgency urinary incontinence (UUI) episodes, and **(C)** urgency episodes; and **(D)** percentage of subjects reporting treatment response at weeks 2 and 12 with fesoterodine 4 mg, fesoterodine 8 mg, or placebo. * $P < .05$ vs placebo; † $P < .05$ vs fesoterodine 4 mg.

mild or moderate severity. Only 1 subject (0.9%) in the fesoterodine 8-mg group and none in the fesoterodine 4-mg or placebo groups discontinued treatment because of dry mouth. Fifteen men experienced treatment-emergent urinary disorders other than urinary retention, including 4 with dysuria (fesoterodine 8 mg, n = 3; placebo, n = 1), 2 with micturition urgency (fesoterodine 4 mg, n = 1; fesoterodine 8 mg, n = 1), and 2 with hematuria (both in the fesoterodine 4-mg group). There was 1 case of enuresis and 1 case of nocturia in the placebo group that were not present at baseline and that were reported as treatment-emergent adverse events.

The LS mean (standard error) changes in PVR were significantly greater, but well below the 50-mL cut-off that is considered clinically relevant,[27] in the fesoterodine 4 and 8 mg groups compared with the placebo group: 9.62 (3.57) and 20.19 (3.61) for fesoterodine 4- and 8-mg, respectively, vs −0.58 (3.44) for placebo. The LS

Table 2. Treatment-emergent adverse events at study end (≥2% in any treatment group)

	No. (%) Subjects		
	Placebo (n = 124)	Fesoterodine 4 mg (n = 120)	Fesoterodine 8 mg (n = 114)
Dry mouth	7 (5.6)	15 (12.5)	43 (37.7)
Constipation	1 (0.8)	3 (2.5)	10 (8.8)
Symptoms suggestive of urinary retention*	1 (0.8)	1 (0.8)	6 (5.3)
Dyspepsia	0	5 (4.4)	1 (0.8)
Hypertension	2 (1.6)	2 (1.8)	4 (3.3)
Dry throat	2 (1.6)	1 (0.8)	3 (2.6)
Dysuria	1 (0.8)	0	3 (2.6)
Upper respiratory tract infection	3 (2.4)	2 (1.7)	2 (1.8)
Headache	5 (4.0)	3 (2.5)	2 (1.8)
Nasopharyngitis	2 (1.6)	4 (3.3)	1 (0.9)
Diarrhea	2 (1.6)	4 (3.3)	1 (0.9)
Dizziness	2 (1.6)	3 (2.5)	1 (0.9)
Sinusitis	3 (2.4)	0	0

* Symptoms suggestive of urinary retention included, but were not restricted to, decreased urine flow and hesitation.

Table 3. Incidence of urinary retention

	No. (%) Subjects		
	Placebo (n = 124)	Fesoterodine 4 mg (n = 120)	Fesoterodine 8 mg (n = 114)
Urinary retention	1 (0.8)*	1 (0.8)†	6 (5.3)‡
Decreased urine flow	0	1 (0.8)	2 (1.8)
Urinary hesitation	0	0	2 (1.8)
PVR > 200 mL	1 (0.8)	1 (0.8)	2 (1.8)

PVR = postvoid residual volume.
* This subject had PVR > 200 mL at last visit (end of treatment), and therefore did not discontinue prematurely.
† This subject had both decreased urine flow and PVR > 200 mL.
‡ Of the 6 subjects in the fesoterodine 8-mg group with urinary retention, only 1 subject was catheterized.

mean change in PVR was significantly greater in the fesoterodine 8-mg group than in the fesoterodine 4-mg group ($P = .035$). A total of 8 subjects had symptoms suggestive of urinary retention (placebo, n = 1; fesoterodine 4 mg, n = 1; fesoterodine 8 mg, n = 6), including 4 subjects with PVR > 200 mL, 3 subjects with decreased urine flow, and 2 subjects with urinary hesitation (Table 3). Only 1 subject, in the fesoterodine 8-mg group, was catheterized.

Overall, 25 men (7.0%) discontinued treatment prematurely because of an adverse event during the treatment phase, including 6 (4.8%) in the placebo group, 8 (6.7%) in the fesoterodine 4-mg group, and 11 (9.6%) in the fesoterodine 8-mg group. Four men, 1 in the fesoterodine 4-mg group (0.8%) and 3 in the fesoterodine 8-mg group (2.6%), were withdrawn from the trials because of urinary retention, defined as PVR > 200 mL or symptoms suggestive of urinary retention.

COMMENT

In this post hoc subanalysis, fesoterodine 8 mg produced significantly greater improvements in all bladder diary measures and a significantly higher treatment response rate vs placebo in men with OAB after 12 weeks of treatment. Fesoterodine 4 mg produced significantly greater improvements vs placebo in most diary endpoints, including median percentage change in the number of micturitions, urgency episodes, and UUI episodes and LS mean change in micturitions and urgency episodes, as well as a significantly higher treatment response rate at week 12. Fesoterodine 8 mg yielded significantly greater improvement in UUI episodes and MVV per micturition compared with fesoterodine 4 mg at week 12. Improvements in diary variables and a higher treatment response rate vs placebo were observed as early as week 2 (first clinical evaluation) in subjects receiving fesoterodine 8 mg and were maintained to the end of the study; UUI episodes were improved at week 2 with fesoterodine 4 mg.

Overall, fesoterodine was well tolerated by men in this study. As expected, adverse events reported with fesoterodine were typical of those associated with antimuscarinics, including dry mouth, constipation, and dyspepsia, and increased in an apparent dose-dependent fashion. The incidence of dry mouth was considerably higher in the fesoterodine groups, particularly the 8-mg group, than in the placebo group, but most occurrences were of mild to moderate severity and only 1 (0.9%) subject in the fesoterodine 8-mg group discontinued because of dry mouth. Constipation was reported in 2.5% and 8.8% of men taking fesoterodine 4 and 8 mg, respectively, compared with 0.8% of men in the placebo group. The low incidence of constipation observed with fesoterodine might reflect a lack of specificity for the muscarinic M_3 subtype, which mediates gastrointestinal motility and predominates over the M_2 subtype in the gastrointestinal tract.[28]

Postvoid residual volume > 200 mL was documented in 4 men, 1 of whom was given placebo. Most episodes of urinary retention, defined as PVR > 200 mL or symptoms suggestive of urinary retention, with fesoterodine occurred in the fesoterodine 8-mg group, in men aged ≥66 years, and within 1-14 days of beginning treatment. Only 1 man (0.9%), who was in the fesoterodine 8-mg group, was catheterized. One and 3 subjects in the fesoterodine 4 and 8 mg groups, respectively, discontinued because of urinary retention, defined as PVR > 200 mL or symptoms suggestive of urinary retention.

The results of this study are consistent with previous reports demonstrating that antimuscarinics effectively reduce OAB symptoms and are generally well tolerated in men.[9-11,18,20] The results from our post hoc analysis of male subjects are also similar to those obtained in the general population in these phase III trials.[22,23] In addition, our results are consistent with those of a pooled analysis of data from the general population of these studies in which the 8-mg dose was significantly better

than the 4 mg dose in decreasing the number of UUI episodes and increasing MVV, although the studies were not powered for this comparison.[25] One exception is that, in one of the individual studies,[22] at the end of treatment, fesoterodine 4 mg was noted to be significantly more effective than placebo in increasing MVV, which was not observed in the present analysis.

These findings are important because OAB symptoms are relatively prevalent in men (11%-16%),[3,4] have a negative effect on measures of health-related quality of life,[3] and may be more bothersome than voiding symptoms in men.[29] Moreover, the apparent dose response observed for several efficacy outcomes is uncommon in parallel-group studies of antimuscarinics that offer multiple doses, and this is the first analysis demonstrating a dose response specifically in men with OAB. Additionally, the onset of efficacy appeared to be earlier with fesoterodine 8 mg compared with fesoterodine 4 mg for most endpoints. Collectively, these data suggest that the availability of 2 doses of fesoterodine will allow clinicians to tailor the dosing regimen to optimize the balance between efficacy and tolerability in men.

This study should be interpreted within the context of its limitations. This was a post hoc analysis of data pooled from 2 clinical trials that were not designed or powered to assess the efficacy of fesoterodine 4 and 8 mg in men alone or to directly compare the 4 and 8 mg doses, so the results must be interpreted with caution. The duration of the trials that provided data for this analysis was 12 weeks. Longer-term data on the efficacy and safety of fesoterodine in men are warranted, although recent data suggest that the risk of acute urinary retention in men treated with antimuscarinics is highest within 30 days of treatment initiation;[30] the results from the present study are consistent with this finding. Additionally, prostate size and prostate-specific antigen levels were not measured during this study, so we cannot assess whether treatment outcomes were different between men with larger vs smaller prostates or higher vs lower prostate-specific antigen levels. Finally, the trials that provided data for this analysis had an exclusion criterion of PVR > 100 mL, but there was no formal assessment of flow rate to guide clinician assessment of the presence of BOO. Therefore, it is possible that some subjects with clinically relevant BOO may have been enrolled, although "clinically relevant BOO" was a specific exclusion criterion. The extent to which the subjects in this study are representative of patients seen in clinical practice is unclear.

CONCLUSIONS

Among men with OAB enrolled in 2 phase III studies, fesoterodine 4 and 8 mg significantly improved most bladder diary variables compared with placebo, and both doses were generally well tolerated and safe. Some of the improvements in OAB symptoms were dose dependent. The availability of 2 doses of fesoterodine allows for dose titration and treatment individualization in men.

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