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1. Fesoterodine treatment after a sub-optimal response to tolterodine ER

Cardozo et al. A randomised controlled trial of fesoterodine in subjects with overactive bladder and suboptimal response to tolterodine extended release: results from the AFTER study [abstract]. Eur Urol Suppl. 2013;12: e740.¹

Kaplan et al. Urgency urinary incontinence response rates in subjects with overactive bladder treated with fesoterodine 8 mg after suboptimal response to tolterodine extended release 4 mg: a randomized, double-blind, placebo-controlled trial [abstract] Neurourol Urodyn. 2013;32(6):abstract #546.²

The efficacy and tolerability of fesoterodine 8 mg in subjects who responded suboptimally to tolterodine ER 4 mg was assessed in a randomized, double-blind, placebo controlled trial. Enrolled subjects with OAB symptoms including UUI were treated with tolterodine ER 4 mg during a 2-week, open-label run-in period. Seventy-one percent of subjects showed a $\leq 50\%$ decrease in UUI episodes (median decrease, 16.7%) and were considered partial responders, whereas 29% of subjects showed a $>50\%$ decrease in UUI during the run-in period (median decrease, 83.3%) were considered tolterodine ER responders. Partial responders were subsequently randomized to treatment with fesoterodine 8 mg or placebo for 12 weeks. Subjects treated with fesoterodine 8 mg had significantly greater reductions in UUI episodes than subjects who received placebo at week 12 (primary endpoint; fesoterodine 8 mg, -2.4 ; placebo, -1.9) urgency episodes, and scores on the PPBC, UPS, and OAB-q Symptom Bother and HRQL scales versus placebo among subjects who previously showed a suboptimal response to tolterodine ER 4 mg ($\leq 50\%$ reduction of UUI episodes during 2-week run-in). Proportions of subjects with 50% and 70% decreases in UUI episodes (70% versus 57% and 59% versus 44%, respectively) were also significantly higher with fesoterodine 8 mg versus placebo at week 12 (all $P < 0.05$).

2. Superiority of Fesoterodine 8 mg Versus Fesoterodine 4 mg in Reducing Urgency Urinary Incontinence Episodes in Subjects with OAB

Chapple et al. Superiority of Fesoterodine 8 mg Versus Fesoterodine 4 mg in Reducing Urgency Urinary Incontinence Episodes in Subjects with Overactive Bladder: Results of the Randomized, Double-Blind, Placebo-Controlled EIGHT Trial. BJU Int. 2014; e-pub (DOI 10.1111/bju.12678).³

The EIGHT study was a 12-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter study. The study consisted of a 2-week single-blind placebo run-in period, followed by a 12-week double-blind treatment. The objective was to demonstrate superior efficacy of 8 mg fesoterodine versus 4 mg of fesoterodine in reducing urgency urinary incontinence (UUI) in patients with overactive bladder (OAB) after 12 weeks of treatment. Eligible patients included those who were aged ≥ 18 years with overactive bladder (OAB) symptoms for ≥ 6 months, ≥ 8 micturitions and ≥ 2 and ≤ 15 urgency urinary incontinence (UUI) episodes/24 hours on baseline diary, and at least moderate bladder-related problems on the Patient Perception of Bladder Condition (PPBC). Demographics were well balanced for all treatment groups.

A total of 4326 subjects were screened and 2012 were randomized of which 1955 received at least one dose of double-blind study drug (386 in placebo group, 790 in fesoterodine 4mg group, and 779 in fesoterodine 8mg group). Those randomized to fesoterodine 8 mg began initial treatment with fesoterodine 4 mg for 1 week, then increased to 8 mg for 11 weeks. At baseline and at Week 12, all patients completed bladder diaries, PPBC, Urgency Perception Scale (UPS), and the Overactive Bladder Questionnaire (OAB-q).

The primary efficacy comparison was the change in the mean number of UUI episodes at Week 12 versus baseline with the primary comparison between fesoterodine 8 mg and fesoterodine 4 mg. The comparison of fesoterodine 8 mg and fesoterodine 4 mg only occurred after a closed-testing procedure where fesoterodine 8 mg was compared to placebo. If the treatment effect of fesoterodine 8 mg versus placebo was significant ($p < 0.0001$) then the treatment difference of fesoterodine 8 mg and 4 mg was assessed ($p = 0.0109$). In addition there was a statistically significant decrease in the mean number of UUI episodes/24 hours at Week 12 relative to baseline for the fesoterodine 4 mg group versus placebo group ($p < 0.0001$). The LS mean decrease from baseline was -3.1 episodes in the fesoterodine 8 mg group, -2.9 episodes in the fesoterodine 4 mg group, and -2.2 episodes in the placebo group (LS Mean Difference = -0.9 between the fesoterodine 8 mg and placebo groups and -0.2 between the fesoterodine 8 mg and 4 mg groups). Additionally, statistically significant improvements in secondary endpoints were seen in the fesoterodine 8 mg group compared to fesoterodine 4 mg or placebo in micturitions, urgency episodes, and in scores on the PPBC, UPS, and all OAB-q total and all sub-domains (concern, coping, sleep and social interaction), and significantly higher diary dry rates in the fesoterodine 8 mg group versus the fesoterodine 4mg and placebo groups (all $P < 0.05$).

Fesoterodine was generally well tolerated with an acceptable safety profile consistent with previous fesoterodine clinical trials. The most commonly reported adverse events included dry mouth and constipation in the placebo (3.4% and 1.8%), fesoterodine 4 mg (12.9% and 1.5%), and fesoterodine 8 mg (26.1% and 4.0%), respectively, most cases were mild or moderate in all treatment groups. The rate of serious adverse events was 2.8% ($n = 11$) in the placebo group, 1.3% ($n = 10$) in the fesoterodine 4 mg group, and 1.3% ($n = 10$) in the fesoterodine 8 mg group.

3. Use in elderly patients

Because the prevalence of OAB increases with age,⁴ more older patients than younger patients are likely to seek treatment for OAB symptoms. However, treatment of OAB in older patients may be complicated by comorbid conditions and polypharmacy. Although the 2 pivotal phase III trials of fesoterodine did not have an upper age limit for enrollment,^{5,6} the mean age of subjects enrolled in these studies was mid-to-late 50s, an age that does not reflect patients considered elderly. Consequently, Pfizer conducted clinical trials in subjects aged ≥ 65 years to define the efficacy and safety profiles of fesoterodine in elderly patients. Results indicate that, overall, fesoterodine provides an efficacious and well-tolerated treatment for OAB symptoms in older patients, including those who meet criteria for vulnerable elderly.

Wagg et al. Flexible-dose fesoterodine in elderly adults with overactive bladder: results of the randomized, double-blind, placebo-controlled study of fesoterodine in an aging population trial. J Am Geriatr Soc. 2013;61:185-193.⁷

Wagg et al. Long-term safety, tolerability and efficacy of flexible-dose fesoterodine in elderly patients with overactive bladder: open-label extension of the SOFIA trial. Neurourol Urodyn. 2013; e-pub (DOI 10.1002/nau.22383).⁸

This 24-week, multicenter study, called SOFIA (Study of Fesoterodine in an Aged Population), consisted of a 12-week, randomized, double-blind, placebo-controlled phase followed by a 12-week, open-label

phase to evaluate the efficacy, safety, and tolerability of fesoterodine in elderly subjects with OAB. Men and women aged ≥ 65 years could enroll in the study if they had self-reported OAB symptoms for ≥ 3 months, including ≥ 8 micturitions per 24 hours, ≥ 3 urgency episodes per 24 hours, and a rating of at least some moderate problems on the PPBC. During the double-blind phase, subjects were randomly assigned to receive fesoterodine 4 mg or placebo once daily, to be taken either in the morning or evening. At weeks 4 and 8, subjects could opt to increase the fesoterodine dose to 8 mg based on treatment response and tolerability; subjects who increased the dose at week 4 could decrease at week 8 (sham dose increases or decreases for placebo). During the open-label phase, all subjects received fesoterodine; subjects given fesoterodine during double-blind treatment maintained their dose, whereas those given placebo were started on fesoterodine 4 mg with an option to increase to 8 mg at weeks 16 or 20. Throughout the 24-week study period, subjects were allowed only 1 dose increase and 1 dose decrease. Efficacy assessments included changes in OAB symptoms recorded in a 3-day bladder diary and changes in scores on several patient-reported outcome measures.

During the double-blind phase, 392 subjects were treated with fesoterodine and 393 received placebo. During the open-label phase, 313 subjects continued treatment with fesoterodine and 341 subjects initially assigned to placebo began treatment with fesoterodine. Approximately equal numbers of men and women were enrolled in the double-blind phase; the mean age of the subjects was 73 years in both groups. Approximately one third of subjects in each group were aged >75 years. Forty-six percent of subjects reported >0 UUI episodes at baseline, and 64% had been receiving treatment with antimuscarinics before the study. The demographic characteristics at baseline of subjects entering the open-label phase were comparable to those in the double-blind phase.

At week 4, 187 (52%) and 246 (66%) of subjects in the fesoterodine and placebo groups opted for dose escalation, respectively. At week 8, 51 (16%) and 30 (9%) of subjects in the fesoterodine and placebo groups opted for dose escalation and 12 (4%) and 10 (3%) de-escalated, respectively. Dosing during the double-blind and open-label phases is summarized in **Table 1**.

Table 1. Dosing during double-blind and open-label phases

| | Double-Blind Fesoterodine | Double-Blind Placebo |
|-------------|--|--|
| Baseline | | |
| 4 mg, n | 392 | 393 |
| Week 4 | | |
| n | 360 | 370 |
| 4 mg, n (%) | 173 (48.1) | 124 (33.5) |
| 8 mg, n (%) | 187 (51.9) | 246 (66.5) |
| Week 8 | | |
| n | 330 | 350 |
| 4 mg, n (%) | 120 (36.4) | 100 (28.6) |
| 8 mg, n (%) | 210 (63.6) | 250 (71.4) |
| | Double-Blind Fesoterodine/Open-Label Fesoterodine | Double-Blind Placebo/Open- Label Fesoterodine |
| Week 12 | | |
| n | 313 | 341 |
| 4 mg, n (%) | 125 (39.9) | 328 (96.2) |
| 8 mg, n (%) | 188 (60.1) | 13 (3.8) |
| Week 16 | | |
| n | 274 | 322 |
| 4 mg, n (%) | 118 (43.1) | 158 (49.1) |
| 8 mg, n (%) | 156 (56.9) | 164 (50.9) |
| Week 20 | | |
| n | 279 | 303 |
| 4 mg, n (%) | 132 (47.3) | 149 (49.2) |
| 8 mg, n (%) | 147 (52.7) | 154 (50.8) |

During the double-blind phase, decreases from baseline to week 12 in urgency episodes per 24 hours (primary endpoint) and several other bladder diary endpoints were significantly greater with fesoterodine compared with placebo (**Table 2**). The median change in UUI episodes among subjects reporting this symptom at baseline was not statistically significantly different for fesoterodine and placebo (−1.00 versus −0.67; $P=0.73$), although this may be attributable to the observation that only 46% of subjects reported UUI at baseline and, among those, the baseline median was <2 UUI episodes per 24 hours in both treatment groups. Compared with placebo, fesoterodine significantly improved OAB-q total HRQL

and Symptom Bother scores, as well as scores on all HRQL domains (all $P<0.05$). The percentage of responders on the Treatment Benefit Scale, PPBC, and UPS were all significantly higher with fesoterodine (all $P<0.0009$); changes in scores on the KHQ and EQ-5D were not significant between fesoterodine and placebo. In this group of older individuals, no clinically relevant changes were seen in the MMSE, a test for cognitive impairment, in either treatment group at the end of 12 weeks of double-blind treatment versus baseline.

During the open-label phase, the treatment response was maintained in the subjects who received fesoterodine during the double-blind phase (**Table 2**). At the end of the open-label phase, the treatment response to fesoterodine in the group given placebo during the double-blind phase was similar to that of the active treatment group at week 12 (**Table 2**).

Table 2. Change from baseline to week 12 and week 24 in bladder diary variables

| | Placebo/Fesoterodine* | | Fesoterodine | |
|--------------------------------|-----------------------|-------------|--------------|-------------------|
| | Baseline | Mean Change | Baseline | Mean Change |
| Week 12 (double blind) | | | | |
| Urgency episodes/24 h | 8.8 | -1.9 | 8.5 | -3.5 [†] |
| Severe urgency episodes/24 h | 4.1 | -1.6 | 3.5 | -2.4 [†] |
| Micturitions/24 h | 12.1 | -0.9 | 11.9 | -1.9 [†] |
| Nighttime micturitions/24 h | 2.9 | -0.3 | 2.8 | -0.5 [†] |
| UUI episodes/24 h [†] | 1.7 | -0.7 | 1.3 | -1.0 |
| Week 24 (open label) | | | | |
| Urgency episodes/24 h | 8.8 | -4.2 | 8.4 | -4.1 |
| Severe urgency episodes/24 h | 4.2 | -2.6 | 3.6 | -2.4 |
| Micturitions/24 h | 12.0 | -2.3 | 11.8 | -2.4 |
| Nighttime micturitions/24 h | 2.9 | -0.6 | 2.7 | -0.7 |
| UUI episodes/24 h [†] | 1.7 | -1.2 | 1.3 | -1.0 |

*During the open-label phase, subjects given placebo during the double-blind phase were switched to fesoterodine.

[†]UUI data are presented as medians, and include only subjects with >0 UUI episodes/24 h at baseline (placebo, n=178; fesoterodine, n=187).

[†] $P<0.01$ vs placebo.

During double-blind treatment, adverse events were reported by 62% and 36% of the fesoterodine and placebo groups, respectively; serious adverse events were reported by <5% of subjects in both groups. During open-label treatment, adverse events were reported by 31% of the fesoterodine group and 48% of the placebo/fesoterodine group; serious adverse events occurred in <5% of subjects in both groups. The most common adverse events reported with fesoterodine during both the double-blind and open-label phases were dry mouth and constipation.

This 24-week study, consisting of both double-blind and open-label treatment, indicates that flexible doses of fesoterodine are efficacious and well tolerated in subjects aged ≥ 65 years. Adverse events were

typical of those reported in other fesoterodine studies, and no new safety concerns were observed in this elderly patient population.

DuBeau et al. Effect of fesoterodine in vulnerable elderly subjects with urgency incontinence: a double-blind, placebo-controlled trial. J Urol. 2013; e-pub (DOI 10.1016/j.juro.2013.08.027).⁹

This was a 12-week, randomized, double-blind, placebo-controlled, multicenter trial conducted in vulnerable elderly patients, defined as those aged ≥ 65 years who scored ≥ 3 on the 13-item VES-13.¹⁰ The VES-13 is a validated measure on which patients self-rate their health, limitations in physical function, and functional disabilities.¹⁰ Patients with VES-13 scores ≥ 3 have more than 4 times the risk of death or functional decline over a 2-year period compared with patients with scores < 3 .

Because this study was the first to evaluate fesoterodine in a vulnerable elderly population, efficacy, safety, and tolerability needed to be assessed using a placebo-controlled design. All patients had self-reported OAB symptoms for ≥ 3 months before screening, including a mean of ≥ 2 UUI episodes per 24 hours and ≥ 8 micturitions per 24 hours as recorded in a 3-day bladder diary. Patients with moderate to very severe cognitive impairment, defined as a MMSE score < 20 , were excluded. Eligible subjects were randomly assigned to treatment with fesoterodine 4 mg or placebo once daily for the first 4 weeks, after which, in consultation with the investigator, the fesoterodine dose could be increased to 8 mg for the remaining 8 weeks (sham dose escalation for placebo). During the last 8 weeks of the study, the fesoterodine dose could be decreased to 4 mg at any time. The primary endpoint was the change from baseline in the mean number of UUI episodes per 24 hours at week 12. Secondary endpoints included the change in the mean number of micturitions per 24 hours, urgency episodes per 24 hours, and absorbent product use per 24 hours, as well as changes in scores on the PPBC and OAB-q. For absorbent product data, a significant qualitative baseline by treatment interaction was found, where treatment effect reversed at the baseline value of 2.5 changes per 24 hours. Therefore, absorbent product data were stratified (≤ 2.5 and > 2.5 changes per 24 hours at baseline) for analysis.

Of 1401 subjects screened, 562 were randomized and received at least 1 dose of study drug (fesoterodine, $n=281$; placebo, $n=281$). The study population was mostly white (86% in both groups) and female ($\geq 80\%$ in both groups). The mean age was 75 years, with approximately 50% of subjects aged ≥ 75 years. Two hundred twenty-six subjects (80%) in the fesoterodine group and 220 (78%) in the placebo group completed the study. A total of 148 (53%) subjects in the fesoterodine group escalated to the 8-mg dose; of these subjects, 125 (84% of those who escalated) completed the study on the 8-mg dose (12 de-escalated, 11 discontinued). A total of 181 (64%) subjects in the placebo group sham escalated; of these subjects, 161 (89% of those who escalated) completed the study on the “higher” dose (3 de-escalated, 17 discontinued).

The decrease from baseline in the number of UUI episodes at week 12 (primary endpoint) was significantly greater with fesoterodine compared with placebo, as was the decrease in the number of micturitions and urgency episodes (secondary endpoints) (**Table 3**). The reduction in the number of absorbent products changed per 24 hours was significantly greater with fesoterodine for subjects with ≤ 2.5 changes per 24 hours at baseline, representing 83.0% of subjects, but not for subjects with > 2.5 changes per 24 hours at baseline (**Table 3**). In a post hoc analysis, the percentage of subjects reporting no UUI episodes at week 12 was significantly greater with fesoterodine versus placebo (51% versus 36%; $P=0.002$).

Table 3. Change from baseline to week 12 in UII episodes and other bladder diary endpoints

| | Placebo | Fesoterodine |
|--|----------------|----------------|
| UII episodes/24 h | | |
| n | 250 | 256 |
| Baseline mean \pm SD | 3.9 \pm 2.2 | 4.1 \pm 2.3 |
| Change from baseline to week 12 | | |
| LS mean \pm SE | -2.2 \pm 0.2 | -2.8 \pm 0.2 |
| LS mean \pm SE difference | | -0.7 \pm 0.2 |
| <i>P</i> value | | 0.0018 |
| Micturitions/24 h | | |
| n | 253 | 258 |
| Baseline mean \pm SD | 12.2 \pm 3.2 | 12.1 \pm 3.1 |
| Change from baseline to week 12 | | |
| LS mean \pm SE | -1.5 \pm 0.2 | -2.3 \pm 0.2 |
| LS mean \pm SE difference | | -0.8 \pm 0.2 |
| <i>P</i> value | | 0.0003 |
| Urgency episodes/24 h | | |
| n | 251 | 256 |
| Baseline mean \pm SD | 10.3 \pm 3.7 | 10.0 \pm 3.5 |
| Change from baseline to week 12 | | |
| LS mean \pm SE | -2.8 \pm 0.3 | -4.2 \pm 0.3 |
| LS mean \pm SE difference | | -1.4 \pm 0.4 |
| <i>P</i> value | | <0.0001 |
| Absorbent product changes/24 h in subjects with \leq2.5 changes/24 h at baseline | | |
| n | 172 | 169 |
| Baseline mean \pm SD | 1.2 \pm 0.6 | 1.4 \pm 0.6 |
| Change from baseline to week 12 | | |
| Mean \pm SD | -0.3 \pm 1.1 | -0.7 \pm 0.8 |
| Mean \pm SE difference | | 0.4 \pm 0.1 |
| <i>P</i> value | | <0.0001 |

Absorbent product changes/24 h in subjects with >2.5 changes/24 h at baseline

| | | |
|---------------------------------|----------------|----------------|
| n | 35 | 35 |
| Baseline mean \pm SD | 3.7 \pm 1.4 | 3.9 \pm 1.2 |
| Change from baseline to week 12 | | |
| Mean \pm SD | -2.1 \pm 2.1 | -2.0 \pm 1.9 |
| Mean \pm SE difference | | 0.2 \pm 0.5 |
| P value | | 0.7437 |

Between-group differences on the PPBC were statistically significant for fesoterodine compared with placebo, with 39% of the fesoterodine group and 29% of the placebo group reporting major improvement at week 12 ($P=0.002$). The change from baseline to week 12 on the OAB-q Symptom Bother scale score was significantly greater with fesoterodine than placebo (LS mean \pm SE, -28.1 ± 1.6 versus -20.5 ± 1.6 ; $P=0.0002$). Improvement of scores on the OAB-q total HRQL scale and the concern and coping domains was significantly greater with fesoterodine than placebo (all $P<0.05$).

Adverse events were reported in 56% of the fesoterodine group and 43% of the placebo group (**Table 4**). Serious adverse events occurred in 8 subjects (3%) in the fesoterodine group and 6 subjects (2%) in the placebo group, none of which was considered treatment-related by the investigators. The most common adverse events were dry mouth and constipation, with most cases mild or moderate. Of the 9 cases of urinary retention in the fesoterodine group, only 3 required bladder catheterization. Three cases of cognitive impairment, 2 of which were considered related to study drug, occurred in the fesoterodine group; fesoterodine was discontinued in 1 of these 3 subjects. Overall, changes on the MMSE from baseline to week 12 were small in both the fesoterodine and placebo groups (LS mean \pm SE, 0.15 ± 0.12 versus 0.33 ± 0.12 ; $P=0.2788$)

Table 4. Summary of adverse events

| | Patients, n (%) | |
|------------------------------------|-----------------|--------------|
| | Placebo | Fesoterodine |
| Evaluable for adverse events | 281 | 281 |
| Subjects with adverse events | 120 (43) | 158 (56) |
| Discontinued due to adverse events | 14 (5) | 26 (9) |
| Most common adverse events | | |
| Dry mouth | 17 (6) | 66 (24) |
| Constipation | 12 (4) | 31 (11) |
| Diarrhea | 7 (3) | 8 (3) |
| Dyspepsia | 1 (1) | 7 (3) |
| Fatigue | 3 (1) | 8 (3) |
| Headache | 5 (2) | 7 (3) |

| | | |
|-------------------|-------|-------|
| Cough | 2 (1) | 7 (3) |
| Urinary retention | 0 | 9 (3) |

Fesoterodine, at doses up to 8 mg, significantly decreased the number of daily UUI episodes and micturitions in vulnerable elderly subjects. Fesoterodine was well tolerated, with no new safety concerns identified in this vulnerable elderly patient population.

4. Patients with nocturnal urgency

Awakening at night to urinate because of nocturnal urgency disrupts sleep and may increase the risk of falls from nighttime trips to the toilet. In a randomized, double-blind, placebo-controlled study, fesoterodine proved beneficial in controlling nocturnal urgency episodes.

Weiss et al. Efficacy and safety of flexible dose fesoterodine in men and women with overactive bladder including nocturnal urinary urgency. *J Urol.* 2013;189:1396-1401.¹¹

This 12-week, double-blind, placebo-controlled, multicenter study evaluated the effects of flexible doses of fesoterodine in subjects with self-reported OAB symptoms for ≥ 3 months, including ≥ 8 micturitions per 24 hours, ≥ 3 urgency episodes per 24 hours, and between ≥ 2 and ≤ 8 nocturnal urgency episodes per 24 hours, as recorded in a 3-day bladder diary. (Nocturnal urgency was defined as a Urinary Sensation Scale rating ≥ 3 recorded in the bedtime section of the bladder diary.) Eligible subjects were treated with fesoterodine 4 mg or placebo once daily for 4 weeks; at week 4, the fesoterodine dosage could be increased to 8 mg once daily, based on patient treatment response and tolerability (sham dose escalation for placebo). After week 4, no further dose adjustments were permitted. Subjects were to take study medication each day within 4 hours of bedtime. Efficacy was assessed through changes in OAB symptoms, as recorded in 3-day bladder diaries completed by the subjects at baseline, week 4, and week 12. Patients completed the OAB-q at baseline and week 12 and the Epworth Sleepiness Scale (a measure of daytime sleepiness) at baseline, week 4, and week 12.

A total of 963 subjects (mean age, 58 years) were randomly assigned to treatment with fesoterodine (n=476) or placebo (n=487); 937 of these subjects (fesoterodine, n=463; placebo, n=474) took at least 1 dose of study medication and were eligible for efficacy analyses.

At week 12, fesoterodine significantly decreased the mean number of nocturnal urgency episodes per 24 hours (primary endpoint) compared with placebo (**Table 5**). Fesoterodine also significantly improved other bladder diary variables, including the number of micturitions, nocturnal micturitions, and urgency episodes per 24 hours (**Table 5**).

Table 5. Change from baseline to week 12 in bladder diary variables

| | Placebo | Fesoterodine |
|--|----------------|----------------|
| Nocturnal urgency episodes/24 h | | |
| n | 445 | 421 |
| Baseline mean \pm SD | 2.9 \pm 1.0 | 2.9 \pm 0.9 |
| Change from baseline to week 12 | | |
| LS mean \pm SE | -1.1 \pm 0.1 | -1.3 \pm 0.1 |

| | | |
|------------------------------------|------------|-------------|
| LS mean ± SE difference | | -0.22 ± 0.1 |
| <i>P</i> value | | 0.003 |
| Nocturnal micturitions/24 h | | |
| n | 443 | 418 |
| Baseline mean ± SD | 3.2 ± 1.1 | 3.2 ± 1.0 |
| Change from baseline to week 12 | | |
| LS mean ± SE | -0.9 ± 1.1 | -1.0 ± 1.2 |
| LS mean ± SE difference | | -0.2 ± 0.1 |
| <i>P</i> value | | 0.011 |
| Micturitions/24 h | | |
| n | 443 | 418 |
| Baseline mean ± SD | 12.3 ± 3.6 | 12.3 ± 3.3 |
| Change from baseline to week 12 | | |
| LS mean ± SE | -1.9 ± 0.1 | -2.4 ± 0.1 |
| LS mean ± SE difference | | -0.6 ± 0.2 |
| <i>P</i> value | | 0.001 |
| Urgency episodes/24 h | | |
| n | 443 | 415 |
| Baseline mean ± SD | 10.0 ± 4.0 | 9.8 ± 3.6 |
| Change from baseline to week 12 | | |
| LS mean ± SE | -2.7 ± 0.2 | -3.5 ± 0.2 |
| LS mean ± SE difference | | -0.8 ± 0.2 |
| <i>P</i> value | | 0.0009 |
| UUI episodes/24 h | | |
| n | 183 | 156 |
| Baseline mean ± SD | 2.2 ± 2.5 | 2.2±2.6 |
| Change from baseline to week 12 | | |
| LS mean ± SE | -1.3 ± 2.0 | -1.4 ± 2.4 |
| LS mean ± SE difference | | -0.2 ± 0.2 |
| <i>P</i> value | | 0.217 |

At week 12, improvement from baseline in the score on the OAB-q Symptom Bother scale was significantly greater with fesoterodine compared with placebo (LS mean ± SE, -20.3 ± 1.0 versus -15.9 ± 0.9; treatment difference, -4.4 ± 1.3; *P*=0.0006). Improvement from baseline to week 12 in scores for the

OAB-q total HRQL scale and the concern, coping, sleep, and social interaction domains was significantly greater with fesoterodine compared with placebo (all $P \leq 0.05$). Improvement from baseline to week 12 in Epworth Sleepiness Scale scores was seen in both treatment groups, but the treatment difference was not statistically significant (LS mean \pm SE change, fesoterodine versus placebo, -2.3 ± 0.2 versus -1.9 ± 0.2).

Adverse events were reported by 41% of subjects in the fesoterodine group and 32% of the placebo group. The most common adverse events were dry mouth (fesoterodine, 21%; placebo, 8%), constipation (3%, 2%), and headache (2%, 1%). Serious adverse events were reported in 1% and 2% of the fesoterodine and placebo groups, respectively, but none was considered related to study medication.

The results of this study indicate that flexible doses of fesoterodine are well tolerated and efficacious in decreasing nocturnal urgency episodes and nocturnal micturitions.

5. Use in men

Ginsberg et al. Efficacy of fesoterodine compared with extended-release tolterodine in men and women with overactive bladder. *BJU Int.* 2013;112:373-385.¹²

In this prespecified subgroup analysis, pooled data from the two 12-week, randomized, double-blind, placebo-controlled, head-to-head (superiority) studies of fesoterodine 8 mg versus tolterodine ER^{13,14} were used to compare the efficacy of these 2 treatments according to gender.

Eligible participants were aged ≥ 18 years with self-reported OAB symptoms for ≥ 3 months and a mean of ≥ 1 UUI episode and ≥ 8 micturitions per 24 hours in 3-day bladder diaries at baseline. Of 676 men randomized to fesoterodine (4 mg for 1 week, followed by 8 mg for 11 weeks), tolterodine ER 4 mg, or placebo once daily, 673 men received at least 1 dose of treatment in the 2 studies (fesoterodine 8 mg, $n=265$; tolterodine ER, $n=275$; placebo, $n=133$) and were included in this analysis. Baseline demographic and clinical characteristics were generally similar in the 3 treatment groups. Seventy-six (11.5%) men discontinued treatment (fesoterodine 8 mg, $n=38$; tolterodine ER, $n=21$; placebo, $n=17$).

The primary efficacy endpoint was the change from baseline to week 12 in the number of UUI episodes per 24 hours. Secondary endpoints included the change from baseline in other bladder diary variables and in scores on the PPBC, UPS, and OAB-q and the diary-dry rate.

At week 12, no significant treatment difference in the mean change from baseline in the number of UUI episodes per 24 hours was demonstrated between any treatment groups. Significant improvements in the mean number of severe urgency episodes per 24 hours ($P=0.035$) and the score on the OAB-q Symptom Bother scale ($P=0.003$) were observed with fesoterodine 8 mg versus tolterodine ER. Compared with placebo, the mean change from baseline in the number of micturitions, urgency episodes, and severe urgency episodes per 24 hours and in the PPBC in men was significantly improved with fesoterodine 8 mg at week 12 (all $P < 0.02$); scores on the OAB-q Symptom Bother and total HRQL scales and all HRQL domains were also significantly improved with fesoterodine 8 mg versus placebo at week 12 (all $P < 0.005$).

Treatment with both active treatments was well tolerated. Dry mouth (21%, 13%, and 5%, respectively) and constipation (5%, 3%, and 1%, respectively) were the most common adverse events in men treated with fesoterodine 8 mg, tolterodine ER 4 mg, and placebo. The incidence of urinary retention was low in all 3 groups (fesoterodine 8 mg, 2%; tolterodine ER, $< 1\%$; placebo, 2%).

The results of this pooled analysis indicate the superiority of fesoterodine 8 mg over tolterodine ER 4 mg for improving the number of severe urgency episodes and symptom bother in men with OAB, including UUI.

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