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Fesoterodine

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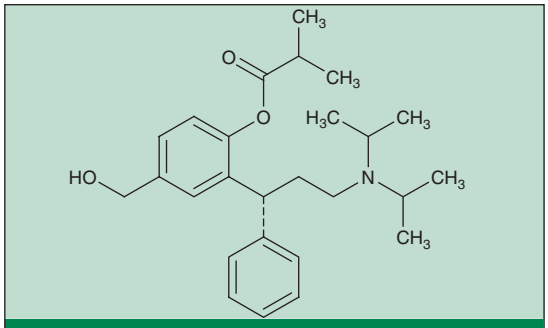
Contents

Abstract

- Fesoterodine is a muscarinic receptor antagonist that is rapidly and extensively converted to the active and more potent metabolite 5-hydroxymethyltolterodine. The drug is approved for once-daily oral administration in patients with overactive bladder syndrome (OAB).
- In two large, 12-week, randomized, double-blind, multicentre, phase III trials, oral fesoterodine 4 or 8 mg once daily improved the symptoms of OAB (frequency of micturition, urgency and urge incontinence) significantly more than placebo.
- Furthermore, significantly more patients receiving fesoterodine 4 or 8 mg once daily had a positive response to therapy than those receiving placebo, as determined by a treatment questionnaire.
- Health-related quality of life was improved to a significantly greater extent in patients with OAB who received fesoterodine 4 or 8 mg once daily than in those who received placebo in a *post hoc* analysis of pooled data from the phase III trials.
- Fesoterodine 4 or 8 mg once daily was generally well tolerated in patients with OAB; the most frequent adverse event was dry mouth, which was generally mild to moderate in severity.

Features and properties of fesoterodine (Toviaz™)			
Indication			
Overactive bladder syndrome			
Mechanism of action			
Muscarinic receptor antagonist			
Dosage and Administration			
Approved dosage		4 or 8 mg/day	
Frequency		Once daily	
Route of administration		Oral	
Pharmacokinetic profile of the fesoterodine metabolite 5-hydroxymethyltolterodine after a single dose of fesoterodine 4 or 8 mg in extensive (EM) and poor (PM) cytochrome P450 2D6 metabolizers			
		4 mg	8 mg
Maximum plasma concentration (ng/mL)	EM PM	1.89 3.45	3.98 6.90
Area under the plasma concentration-time curve (ng • h/mL)	EM PM	21.2 40.5	45.3 88.7
Terminal elimination half-life (h)	EM PM	7.31 7.31	8.59 7.66
Adverse events			
Most common		Dry mouth	



Fesoterodine

Overactive bladder syndrome (OAB) is a chronic and often debilitating condition that is characterized by symptoms of urinary urgency, with or without urinary incontinence, and is often accompanied by frequency and nocturia.[1] Reports of prevalence vary, but based on the above definition, the overall prevalence in over 19 000 men and women aged ≥18 years in several European countries and Canada was 11.8% and increased with increasing age.[2]

The aetiology of OAB is not clear, but is thought to involve activation of the muscarinic receptors in the bladder via release of acetylcholine from postganglionic parasympathetic nerves.[3] Treatment may include behavioural and surgical interventions, but antimuscarinic (anticholinergic) drugs are usually the mainstay of therapy.[1] These agents have demonstrated efficacy in patients with OAB but are also associated with anticholinergic adverse effects.[4] Attempts to improve tolerability have centred on the development of drugs that target specific receptors and formulations that regulate the release of active drug.[4]

Fesoterodine extended-release (Toviaz™) [hereafter referred to as fesoterodine] is an oral, once-daily antimuscarinic drug recently approved in several countries for the treatment of OAB. This profile summarizes the pharmacological properties of the drug and reviews its use in patients with OAB.

Medical literature on the use of fesoterodine was identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Health | Adis). Additional references were identified from the reference lists of published articles.

1. Pharmacodynamic Profile

- Fesoterodine acts as a prodrug and is rapidly converted to its active metabolite 5-hydroxymethyltolterodine (5-HMT) [also known as SPM 7605] by non-specific esterases.[5] Both agents are muscarinic receptor antagonists, but 5-HMT is more potent than the parent drug and is predominantly responsible for the antimuscarinic activity of fesoterodine.[6,7]
- Fesoterodine and 5-HMT are non-selective for the various muscarinic receptor subtypes. In receptor binding studies using membrane preparations of Chinese hamster ovary cells expressing human muscarinic receptors, the mean binding affinities (Ki) of fesoterodine for muscarinic receptor subtypes M_1, M_2, M_3, M_4 and M_5 were 8.0, 7.7, 7.4, 7.3 and 7.5 nmol/L, respectively, and the corresponding Ki values for 5-HMT were 9.5, 9.2, 8.9, 8.7 and 9.2 nmol/L.[8] Multiple muscarinic receptor subtypes exist in normal human bladder mucosa and detrusor membrane; the majority are M_2, with smaller populations of M_1, M_3 and M_5 receptors.[9]
- In an *in vitro* study of rat bladder strips, fesoterodine and 5-HMT (1 μmol/L to 1 mol/L) demonstrated competitive antagonism, as evidenced by a rightward shift of the concentration-response curve for carbachol-induced contractions without a significant depression of the maximum.[8]
- Contractions of rat bladder strips induced by electrical field stimulation were inhibited in a dose-dependent manner by fesoterodine and 5-HMT, with similar potency to that demonstrated with oxybutynin and atropine.[8] Fesoterodine 0.1 μmol/L and 5-HMT 0.1 μmol/L caused 46% and 45% inhibition of contractions compared with 34% and 40% with oxybutynin 0.1 μmol/L and atropine 0.1 μmol/L.[8]
- Low doses of intravenous fesoterodine and 5-HMT (0.01 mg/kg) caused significant ($p < 0.05$) increases from baseline in healthy rat bladder capacity and micturition intervals, and significantly ($p < 0.01$) reduced micturition pressure compared with baseline.[8] Higher doses (0.1 and 1.0 mg/kg) did not further decrease micturition pressure, but

bladder capacity and micturition intervals were unchanged at 0.1 mg/kg and decreased ($p < 0.05$) at 1.0 mg/kg. Residual volume was not significantly affected by any of the three fesoterodine and 5-HMT doses.[8]

- Oral fesoterodine did not affect myocardial repolarization compared with placebo.[10] ECGs of 256 healthy volunteers were obtained at 12 timepoints on day 0 (baseline) and on days 1 and 3 after receiving once-daily fesoterodine 4 or 28 mg, moxifloxacin (control) or placebo for 3 days in a double-blind, parallel-group study. Corrected QT interval changes from baseline with both fesoterodine dosages were not significantly different from those with placebo.[10]

2. Pharmacokinetic Profile

This section summarizes pharmacokinetic data from the manufacturer's prescribing information[6,7] and from a randomized, nonblind, crossover study in healthy volunteers following single oral doses of fesoterodine 4, 8 or 12 mg while fasting, or 8 mg with food.[11]

- After oral administration, fesoterodine is rapidly and extensively hydrolyzed by nonspecific plasma esterases to form the active metabolite 5-HMT; metabolism is so rapid that the parent drug cannot be detected in plasma.[6,7]
- After ascending single or multiple oral daily doses (4–28 mg) of fesoterodine, 5-HMT demonstrated dose-proportional pharmacokinetics.[6,7] The plasma protein binding of 5-HMT is low (≈50%). The time to (t_{max}) maximum plasma concentration (C_{max}) of 5-HMT is about 5 hours, and multiple doses do not result in accumulation.
- Metabolism of 5-HMT is primarily via the cytochrome P450 (CYP) enzymes CYP2D6 and CYP3A4.[6,7] In CYP2D6 poor metabolizers, the 5-HMT C_{max} was increased by about 1.7-fold compared with extensive metabolizers. After a single oral dose of fesoterodine 4 mg, the 5-HMT C_{max} was 1.89 ng/mL in extensive metabolizers and 3.45 ng/mL in poor metabolizers. After a single dose of fesoterodine 8 mg, the corresponding C_{max} values were 3.98 and 6.90 ng/mL.[6,7]
- In CYP2D6 poor metabolizers, the 5-HMT area under the plasma concentration-time curve from time zero up to the last measurable concentration (AUC) was increased 2-fold compared with extensive metabolizers.[6,7] After a single oral dose of fesoterodine 4 mg, the 5-HMT AUC was 21.2 ng • h/mL in extensive metabolizers and 40.5 ng • h/mL in poor metabolizers. After a single dose of fesoterodine 8 mg, the corresponding AUC values were 45.3 and 88.7 ng • h/mL.[6] The t_{max} was unchanged in poor metabolizers compared with extensive metabolizers.[6,7]
- After oral administration of fesoterodine, about 70% of the dose is excreted renally as metabolites, and a small amount is excreted in the faeces (7%).[6,7] The terminal elimination half-life ($t_{1/2\beta}$) of 5-HMT after oral administration is not affected by CYP2D6 status.[6] In poor and extensive metabolizers, the $t_{1/2\beta}$ was 7.31 hours after a single dose of fesoterodine 4 mg and 8.59 hours after a single dose of fesoterodine 8 mg.
- Coadministration of food does not affect the pharmacokinetics of fesoterodine in a clinically significant manner.[11]
- The pharmacokinetic profile of fesoterodine is not altered to a clinically significant extent by sex or age; the pharmacokinetics of the drug have not been assessed in children.[6,7] Furthermore, there were no apparent differences in the pharmacokinetics of fesoterodine between Caucasian and Black healthy volunteers.[6]
- In patients with moderate (Child-Pugh B) hepatic impairment, the total exposure to 5-HMT was about 2-fold higher than that of healthy volunteers.[6] No dosage adjustment is recommended in patients with mild to moderate hepatic impairment, but because data are insufficient, fesoterodine is not recommended in patients with severe (Child-Pugh C) hepatic impairment.[6]
- Exposure to 5-HMT is increased by up to 1.8-fold in patients with mild to moderate renal impairment (creatinine clearance [CL_{CR}] of 30–80 mL/min [1.8–4.8 L/h]) and by 2.3-fold in patients with severe renal impairment (CL_{CR} of <30 mL/min [<1.8 L/h]).[6] No dosage adjustment is

required in patients with mild to moderate impairment, but doses of fesoterodine above 4 mg are not recommended in patients with severe renal impairment.

- Exposure to 5-HMT is increased when fesoterodine is coadministered with potent CYP3A4 inhibitors, such as ketoconazole, itraconazole and clarithromycin, in CYP2D6 poor and extensive metabolizers. As a result, doses of fesoterodine above 4 mg are not recommended in combination with these agents.[6]

3. Therapeutic Efficacy

The efficacy of oral once-daily fesoterodine 4 or 8 mg in patients with OAB has been evaluated in two large, randomized, double-blind, placebo-controlled, multicentre, phase III trials.[12,13] Results of phase II, placebo-controlled studies had previously demonstrated the efficacy of fesoterodine 4, 8 or 12 mg/day in patients with OAB.[14,15]

In the phase III studies, one of which was performed in the US[12] and the other predominantly in Europe,[13] eligible patients were aged ≥18 years and had been experiencing non-neurogenic OAB with or without urge incontinence for ≥6 months. The frequency of micturition was required to be at least eight voids in 24 hours and patients were also required to experience urgency episodes at least six times or urge incontinence at least three times on 3 days during the run-in period.[12,13] Most patients were female (≈78%) and the mean age was similar in both studies (59[12] and ≈57[13] years). The mean time from diagnosis of OAB was 8–10 years, and approximately half of the patients in the US study[12] and about 40% of patients in the European study[13] had received previous drug therapy for their condition.

Both trials incorporated a 2-week placebo run-in period followed by 12 weeks' treatment, after which patients had the option to continue in a long-term, open-label study or complete a 2-week safety follow up.[12,13] During the treatment phase, patients received placebo (n = 271[12] and 283[13]), fesoterodine 4 mg once daily (n = 282[12] and 272[13]) or fesoterodine 8 mg once daily (n = 279[12] and 287[13]). The European study included a fourth treatment arm of tolterodine extended release (ER) 4 mg once daily (n = 290) as an active control (i.e. it was not designed to compare the efficacy of fesoterodine with tolterodine).[13]

The primary efficacy endpoint was the change from baseline to the end of treatment in micturition frequency in 24 hours.[12,13] Efficacy was assessed by a 3-day diary completed by the patient during the run-in period and prior to subsequent visits. Co-primary variables included the change in the number of episodes of urge incontinence in 24 hours compared with baseline, and patient assessment of overall treatment response, which was derived from a 4-category treatment benefit scale (from 1 = greatly improved to 4 = worsened condition); the response was 'yes' if the answer was 1 or 2, and 'no' if the answer was 3 or 4.[12,13]

The impact of fesoterodine on health-related quality of life (HR-QOL) was evaluated in a *post hoc* analysis of pooled data from both of the phase III trials (n = 1903).[12,13] Evaluations were based on the King's Health Questionnaire (KHQ; assesses nine domains including severity/coping, emotions, role limitations, physical limitations, social limitations, sleep/energy, personal relationship, incontinence impact and general health perception), the International Consultation on Incontinence Questionnaire short form (ICIQ-SF; assesses the effects of urinary frequency and urine leakage on daily life), a 6-point Likert scale (0 = no problem to 5 = very severe problems) and the self-reported 4-point treatment benefit scale described perviously.[16,17]

Clinical Response

- Fesoterodine 4 or 8 mg once daily was significantly more effective than placebo in treating the symptoms of OAB.[12,13] At the end of treatment, the reduction in the number of micturitions in 24 hours was significantly greater in patients receiving either dosages of fesoterodine than in those receiving placebo in both studies (figure 1).[12,13] For example, in the US study, the mean reduction from baseline in the number of micturitions in 24 hours in patients receiving placebo versus fesoterodine 4 or 8 mg

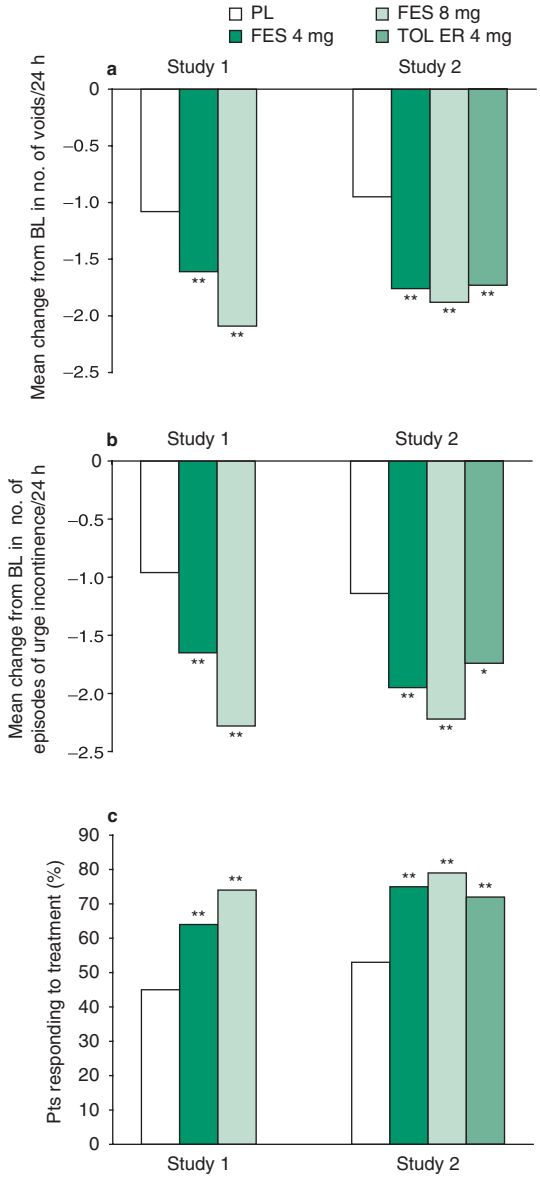


Fig. 1. Efficacy of oral fesoterodine (FES) in patients (pts) with overactive bladder syndrome. Results of two randomized, double-blind, phase III, 12-week studies in which pts (n = 800 evaluable in study 1[12] and n = 1103 evaluable in study 2[13]) received FES 4 or 8 mg once daily (od) or placebo (PL); study 2 included an active-control arm of tolterodine extended release (TOL ER) 4 mg od.[13] Primary endpoints included (**a**) the reduction from baseline (BL) in the mean number of voids per 24-hour period, (**b**) the reduction in the mean number of episodes of urge incontinence per 24-hour period, both assessed over a 3-day period at study end, and (**c**) treatment response derived from a 4-category pt-assessed treatment benefit scale. * $p < 0.01$, ** $p \leq 0.001$ vs PL.

once daily was 1.1 versus 1.6 and 2.1 ($p < 0.001$ for both active treatment groups vs placebo) [corresponding baseline mean values were 12.2, 12.9 and 12.0].[12]

- The number of episodes of urge incontinence experienced in 24 hours was reduced from baseline significantly ($p \leq 0.001$) more in patients receiving fesoterodine 4 or 8 mg once daily than in those receiving placebo in both phase III studies (figure 1).[12,13] For example, in the European study, the mean number of episodes of urge incontinence in patients receiving placebo, fesoterodine 4 or 8 mg once daily or tolterodine ER 4 mg once daily decreased by 1.1, 2.0, 2.2 ($p \leq 0.001$ vs placebo for both comparisons) and 1.7 ($p = 0.008$ vs placebo) [corresponding baseline mean number of episodes were 3.7, 3.8, 3.7 and 3.8].[13]

- Response to treatment questionnaires demonstrated a significantly greater treatment response in patients receiving fesoterodine 4 or 8 mg once daily than in those receiving placebo in both phase III studies.[12,13] The percentage of patients achieving a positive response to therapy in the placebo, fesoterodine 4 or 8 mg once-daily treatment groups was 45%, 64% and 74%, respectively, in the US study,[12] and 53%, 75% and 79% in the European study (with a 72% response rate in tolterodine ER recipients) [$p < 0.001$ vs placebo for all comparisons].[13]

- Once-daily fesoterodine 4 or 8 mg was also significantly more effective than placebo in evaluations of secondary endpoints in both studies.[12,13] For example, the mean number of urgency episodes were improved significantly ($p < 0.01$) more with both dosages of fesoterodine than with placebo. Compared with placebo, both dosages of fesoterodine in the European study,[13] and the 8 mg dosage in the US study,[12] significantly ($p < 0.001$) increased the mean volume voided per micturition.

- Once-daily fesoterodine 4 or 8 mg was associated with a greater number of continent days per week than placebo in both studies.[12,13] In the US study, the mean number of continent days each week in the placebo, fesoterodine 4 and 8 mg groups increased from baseline means of 0.6, 0.7 and

0.7 days by 1.3, 2.3 and 2.8 days, respectively ($p < 0.001$ for both fesoterodine dosages vs placebo).[12] In the European study, corresponding baseline means of 0.8, 0.8 and 0.6 days increased by 2.1, 2.8 ($p = 0.007$ vs placebo) and 3.2 ($p < 0.001$ vs placebo) days.[13]

- *Post hoc* analyses of the phase III trials suggest that fesoterodine 8 mg once daily may provide additional benefit compared with fesoterodine 4 mg once daily[18] or tolterodine ER 4 mg once daily.[19] After 12 weeks' treatment, the co-primary endpoints of episodes of urge incontinence in 24 hours and treatment response were improved significantly ($p < 0.05$) more with fesoterodine 8 mg once daily than with fesoterodine 4 mg once daily,[18] and in a subgroup analysis of patients who were incontinent at baseline, these same endpoints were improved significantly ($p < 0.05$) more with fesoterodine 8 mg once daily than with tolterodine ER 4 mg once daily.[19]

Health-Related Quality of Life

- Overall, in the *post hoc* analysis of pooled data from both phase III trials, HR-QOL improved significantly more in patients with OAB receiving fesoterodine 4 or 8 mg once daily than in those receiving placebo.[16] Compared with placebo, fesoterodine 8 mg once daily was associated with significant ($p < 0.01$) improvements in eight of nine domains of the KHQ (i.e. all except general health perception), and fesoterodine 4 mg once daily and tolterodine ER 4 mg once daily were associated with significant improvements ($p < 0.01$) in seven of nine domains (i.e. all except general health perception and personal relationships).[16]
- Two KHQ domains (severity/coping and emotions) were improved significantly ($p < 0.05$) more with fesoterodine 8 mg once daily than with fesoterodine 4 mg once daily, but there were no statistically significant differences in any domains between fesoterodine 4 or 8 mg once daily and tolterodine ER 4 mg once daily.[16] Improvements considered meaningful to the patients, or minimally important differences (i.e. the change from baseline was ≥5 points) were seen in all active-treatment groups in all but one KHQ domain (general health perception).[16]
- The ICIQ-SF score was improved from baseline (baseline scores ranged from 10 to 12 on the 21-point scale) significantly more with all active treatments than with placebo ($p < 0.001$) and differences between active treatment groups were not statistically significant.[16]
- Likert scale scores at the end of the study ranged from 2.3 to 2.8 (mean baseline score was ≈3.6).[16] Significantly more subjects had an improvement of ≥2 points with fesoterodine 4 mg (33%), fesoterodine 8 mg (38%) and tolterodine ER 4 mg (34%) compared with placebo (21%) [$p < 0.001$ for all].[16]
- A positive treatment response was reported by significantly more patients receiving fesoterodine 4 or 8 mg once daily than those receiving placebo ($p < 0.001$).[16] This improvement was evident at 2 weeks and was maintained through to study end.

4. Tolerability

This section summarizes the tolerability of oral fesoterodine 4 and 8 mg once daily in patients with OAB as reported in two large, phase III studies (see section 3 for study design details).[12,13]

- Fesoterodine 4 and 8 mg once daily was generally well tolerated and the number of patients who discontinued therapy due to adverse events was low in both trials.[12,13] For example, in the US trial, 4%, 6% and 9% of patients receiving placebo, fesoterodine 4 or 8 mg once daily, respectively, discontinued therapy due to an adverse event,[12] and in the European study, the corresponding incidence of patient withdrawals was 2%, 3% and 5% (and 3% with tolterodine ER 4 mg once daily).[13]
- The most frequent adverse event in all treatment groups of both studies was dry mouth, which was generally mild to moderate in severity.[12,13] In the US trial, dry mouth was reported by 7%, 16% and 36% of patients receiving placebo or fesoterodine 4 or 8 mg once daily, and this event led to treatment discontinuation in 1% of patients receiving fesoterodine 4 mg and 2% of patients receiving fesoterodine 8 mg.[12]

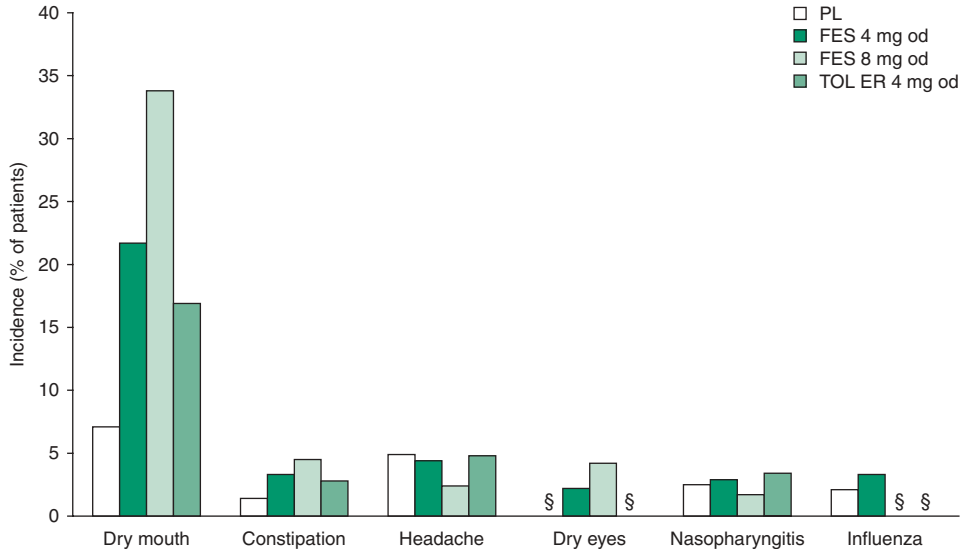


Fig. 2. Tolerability of fesoterodine (FES) 4 or 8 mg once daily (od). Treatment-emergent adverse events occurring in >3% of patients with overactive bladder syndrome who received od FES 4 mg (n = 272), FES 8 mg (n = 287), tolterodine extended release (TOL ER; n = 290) or placebo (PL; n = 283) in a 12-week, randomized, double-blind, multicentre, phase III trial.[13] § = incidence <1%.

• Other adverse events commonly associated with treatment included constipation, headache and dry eyes.[12,13] Treatment-emergent adverse events reported in the European trial are summarized in figure 2.[13]

• Urinary retention requiring catheterization occurred in one patient in the European trial,[20] but mild to moderate urinary retention occurred in ten patients in the US study (none required catheterization), four (1%) in the fesoterodine 4 mg once-daily group and six (2%) in the fesoterodine 8 mg once-daily group; one male patient receiving placebo developed severe urinary retention.[12]

• Overall, fesoterodine treatment was not associated with any clinically relevant changes in vital signs, such as heart rate or blood pressure, or in laboratory parameters or ECG recordings.[12,13] Mean changes in heart rate were similar in fesoterodine treatment groups in both studies.[12,13] In the European study, the mean changes from baseline in heart rate with placebo, fesoterodine 4 or 8 mg once daily, or tolterodine ER 4 mg once daily were 0.8, 3.3, 3.9 and 2.8 beats per minute, respectively.[13]

5. Dosage and Administration

Fesoterodine is indicated for the treatment of OAB to relieve symptoms of urge urinary incontinence, urgency and frequency.[6,7] The recommended dosage is 4 or 8 mg orally once daily.

Dosages of fesoterodine greater than 4 mg/day are not recommended in patients taking potent CYP3A4 inhibitors such as ketoconazole (section 2).[6,7] Local prescribing information should be consulted for information regarding other specific patient populations, contraindications and precautions.

6. Fesoterodine: Current Status

Fesoterodine is approved in several countries worldwide, including the US and the EU, for the treatment of OAB. In large, well designed clinical trials, fesoterodine 4 or 8 mg once daily was significantly more effective than placebo in improving the symptoms associated with OAB. Fesoterodine was also associated with improved HR-QOL compared with placebo and was generally well tolerated.

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