

Fesoterodine for the treatment of urinary incontinence and overactive bladder

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Abstract: Overactive bladder (OAB) is a highly prevalent condition, affecting males and females. The prevalence increases with age. Behavioral therapy and antimuscarinic therapy remain the first-line therapies for management of OAB. Despite improvements in symptoms, persistence with antimuscarinic therapy has remained low. Multiple factors including patient expectations, adverse effects and cost may affect persistence. Fesoterodine is one of the newest antimuscarinic agent approved for the management of OAB. It is unique in that it shares the same active metabolite as tolterodine, 5-hydroxymethyltolterodine (5-HMT); however, this conversion is established via ubiquitous esterases and not via the cytochrome P450 system, thus providing a faster and more efficient conversion to 5-HMT. Fesoterodine is available in 2 doses, 4 mg and 8 mg. Clinical trials have established a dose response relationship in efficacy parameters as well as improvements in quality of life. As with all antimuscarinics, dry mouth and constipation are the more common side effects. A combination of medical therapy and behavioral therapy improves the overall outcome in management of OAB. Dose flexibility may help improve efficacy outcomes and patient education on the management of common adverse effects may improve tolerability with these agents.

Keywords: overactive bladder, antimuscarinic agent, esterase, 5-HMT, fesoterodine

Introduction

Overactive bladder (OAB) is a syndrome complex composed the following symptoms, urgency with or without urgency urinary incontinence (UUI), often in the presence of urinary frequency and nocturia. The term, developed by the International Continence Society, is suggestive of underlying detrusor overactivity, but may be related to other forms of urethrovvesical dysfunction. The term in its strict sense, refers to idiopathic OAB, a condition that occurs in the absence of other conditions that may cause or mimic the symptoms.¹ OAB is a chronic condition that has a significant impact on health related quality of life and may require life-long treatment.^{2,3}

Epidemiologic studies throughout the world have highlighted the prevalence of this condition. The prevalence rates in the United States and Europe range from 12% to 17%. The prevalence of OAB is similar in males and females, and the prevalence increases with age in both sexes.⁴⁻⁶ Despite the high prevalence, only a small percentage of patients are evaluated and treated.⁴ A variety of factors, both physician and patient-related may affect this apparent under-diagnosis and under-treatment.

OAB has a huge impact on quality of life. However, the impact of OAB extends well beyond its impact on quality of life (QOL). Individuals with OAB are at greater risk for urinary tract infections, may have altered sleep, have a greater risk for depression⁷

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and in those with associated urinary incontinence, a greater likelihood of perineal dermatitis. Elderly women with OAB and urinary incontinence are at greater risk for falls and fractures, 26% and 34 %, respectively.^{8,9} In 1995 the amount spent for tangible OAB-related care was US\$12.6 million in the United States.^{10,11} A recent population-based survey was used to calculate disease-specific total costs for OAB for individuals who responded to the survey as having “often” OAB symptoms. The disease specific cost of OAB was estimated at US\$24.9 billion.¹² This economic burden can only be expected to rise as our population ages and grows.

The management of OAB symptoms has relied primarily on pharmacologic therapy with or without behavioral therapy. Antimuscarinic agents are the only approved agents for the management of OAB. Their efficacy in decreasing OAB symptoms and improving QOL has been demonstrated.¹³ Historically, the use of antimuscarinic therapy has been limited by the presence of intolerable side effects and lack of sufficient response in some individuals. Alterations in drug formulations such as once daily dosing, dose flexibility, and medications with greater selectivity for muscarinic receptors in the bladder as opposed to other areas in the body have improved the tolerability profile and ease of use of these agents. Yet, many patients remain on therapy for less than a year. Reasons for the lack of continued use may include insufficient treatment response, unacceptable tolerability, and cost. Identifying the patient’s treatment goals and ensuring that they are reachable goals, is important to the success of antimuscarinic therapy. In addition, proactively managing potential adverse effects may also decrease future discontinuation rates.

Currently, there are 11 different formulations of antimuscarinic agents approved by the FDA for the pharmacologic management of OAB (Table 1). Fesoterodine is one of the most recent antimuscarinic agents to be approved by the FDA. All of these agents are efficacious in the management of OAB, decreasing micturition frequency, urgency severity and urgency incontinence episodes and increasing the volume voided with each micturition. Comparisons of efficacy between the agents are limited by the lack of a significant number of head to head trials. Differences, albeit in some cases subtle, exist between the agents in their delivery systems, metabolism, dose flexibility, and side effect profiles. These differences may allow for prescribing variability depending on patient’s underlying medical conditions and provides for alternative agents in the setting of poor tolerability and/or efficacy with the initial antimuscarinic therapy.

Table 1 Currently approved antimuscarinic agents for overactive bladder

Generic name	Brand name
Oxybutynin	Ditropan
Oxybutynin extended release	Ditropan XL
Oxybutynin patch	Oxytrol
Oxybutynin gel	Gelnique
Tolterodine immediate release	Detrol
Tolterodine extended release	Detrol LA
Solifenacin	Vesicare
Darifenacin	Enablex
Tropium chloride immediate release	Sanctura
Tropium chloride extended release	Sanctura XR
Fesoterodine	Toviaz

Pathophysiology of OAB and rationale for antimuscarinic agents

The cause of idiopathic OAB is not known. Neurogenic, myogenic and combined etiologies have been proposed.¹⁴ Historically, emphasis was placed on the role of the efferent pathway in OAB symptoms. However, abnormalities in the afferent pathway and/or in the central nervous system have been proposed as other possible etiologies of OAB.¹⁵ The muscarinic receptor has been the major peripheral pharmacological target in treating OAB.¹⁶ In the efferent pathway, acetylcholine, released from parasympathetic presynaptic nerve terminals binds to muscarinic receptors in the detrusor muscle to stimulate a detrusor contraction. Although there are 5 different muscarinic receptors located throughout the body (M1–M5),¹⁶ in the bladder, the M2 and M3 receptors predominate. The M2 receptor accounts for 80% of the muscarinic receptors in the detrusor M3 20%.¹⁶ The M3 receptor appears to have the primary role in normal detrusor contraction. M2 receptors appear to indirectly reverse sympathetically mediated smooth muscle relaxation. In certain diseased states, M2 receptors may also contribute to direct smooth muscle contraction.¹⁷ More recently muscarinic receptors have been identified in the urothelium and suburothelium. The role of these muscarinic receptors is not well understood but it is theorized that they may play a role in afferent pathway mediated OAB symptoms.^{18,19}

Pharmacology and pharmacokinetics of fesoterodine

Fesoterodine is one of the newer antimuscarinic agents approved for the treatment of OAB. It is unique in that it shares the same active metabolite as tolterodine. A matrix

platform is used for the extended release delivery of once daily fesoterodine. Upon ingestion, the outer polymer layer swells to form a gel layer surrounding the tablet which controls the release of fesoterodine, thus the tablet cannot be cut crushed or chewed.²⁰ Taking the drug in a fed or fasted state does not appear to have a significant effect.^{20,21} The metabolism of fesoterodine to the active metabolite, 5-HMT, is via rapid hydrolysis by ubiquitous, non-specific esterases which are present throughout the body.^{20,22–24} Tolterodine is also metabolized to 5-HMT, however this is via the cytochrome P450 system. The metabolism of fesoterodine is rapid and extensive, such that fesoterodine cannot be detected in plasma after oral administration.^{20,23} Thus, fesoterodine is a pro-drug.²⁵ Esterases are consistent among individuals, and their activity is not affected by other drugs, thus eliminating two sources of variability in exposure to the drug among different patients.^{26,27} 5-HMT has linear and dose-proportional pharmacokinetics. 5-HMT is eliminated via one of three routes, it is metabolized in the liver to inactive metabolites by the CYP3A4 or CYP2D6 pathway^{28,29} and approximately 16% of 5-HMT is excreted unchanged in the urine.²⁰ Fesoterodine is available in 2 doses, 4 mg and 8 mg. Studies have demonstrated a dose-dependent response with fesoterodine in the reduction of OAB symptoms.^{30,31}

Efficacy of fesoterodine

Two phase III multicenter, randomized, double-blind, placebo-controlled studies were performed to assess the clinical efficacy, safety and tolerability of once-daily fesoterodine in patients with OAB.^{32,33} All subjects had increased urinary frequency and urgency and/or UUI. The primary efficacy variable was a change from baseline to week 12 in micturitions per 24 hours. Co-primary endpoints included change from baseline to week 12 in UUI episodes per 24 hours and treatment response (“yes” or “no”, based on a 4-point treatment benefit scale). Secondary efficacy variables included mean volume voided per micturition, continent days per week and number of urgency episodes. Patients were randomized to placebo, 4 mg of fesoterodine, and 8 mg fesoterodine in the US study,³² whereas in the European study there was an active control arm, tolterodine extended release (ER) 4 mg.³³

US study

A total of 836 subjects were randomized and included in the full analysis set population, 76% of whom were female. The mean age was 59 years (range 21 to 91 years). Approximately 50% of the subjects had received prior OAB treatment and

81% of the patients were incontinent at the time of placebo run-in. Treatment with 4 mg and 8 mg FESO resulted in statistically significant and clinically relevant improvements compared to placebo in the 2 co-primary endpoints ($P < 0.05$). In addition, the mean change from baseline in the number of micturitions and UUI episodes per 24 hours was significantly improved with both doses of fesoterodine compared to placebo. Analysis of secondary endpoints demonstrated significant improvements with 4 mg of fesoterodine compared to placebo for mean change from baseline in urgency episodes and continent days per week (each $P < 0.001$), whereas 8 mg of fesoterodine was significantly better than placebo for mean volume voided per micturition, number of urgency episodes, number of daytime micturitions and continent days per week (each $P < 0.001$)³² (Table 2).

European study

A total of 1132 patients were enrolled and received study medication. Similar to the US study, the mean age was 57 years and most patients were women (80%) with 75% to 81% of subjects reporting urge urinary incontinence on the baseline diary. The mean number of micturitions was significantly reduced from baseline for subjects taking tolterodine ER 4 mg, fesoterodine 4 mg and fesoterodine 8 mg compared to placebo ($P < 0.001$ for each). The mean reduction from baseline in urge urinary incontinence episodes per 24 hours was significantly greater for tolterodine ER ($P = 0.008$), fesoterodine 4 mg ($P = 0.001$) and fesoterodine 8 mg ($P < 0.001$) compared to placebo. The mean volume voided was also significantly increased for tolterodine ER ($P = 0.002$), fesoterodine 4 mg ($P < 0.001$), fesoterodine 8 mg ($P < 0.001$) compared to placebo. Statistically significant reduction in the number of UUI episodes per 24 hours were seen with tolterodine ER ($P = 0.004$), fesoterodine 4 mg ($P = 0.002$) and 8 mg fesoterodine ($P < 0.001$), whereas significant increases in the number of continent days per week were seen with 4 mg fesoterodine ($P = 0.007$) and 8 mg fesoterodine ($P < 0.001$) compared to placebo³³ (Table 2).

Post-hoc analyses

Female subjects

A post-hoc analysis of pooled data from the 2 clinical trials involving 1548 women was performed to assess the efficacy and tolerability of fesoterodine in women. In this analysis, fesoterodine 8 mg was significantly more efficacious than fesoterodine 4 mg and tolterodine ER 4 mg in improving UUI episodes and continent days per week.³⁴

Table 2 Phase III clinical trials – efficacy results²⁰

Parameter	Placebo Euro	Fesoterodine 4 mg Euro	Fesoterodine 8 mg Euro	Placebo US	Fesoterodine 4 mg US	Fesoterodine 8 mg US
Micturitions/24 h						
Baseline	12.0	11.6	11.9	12.2	12.9	12.0
Mean change	-0.95	-1.76*	-1.88*	-1.08	-1.61*	-2.09*
Median % change	-11.1	-16.7*	-18.6*	-6.9	-14.9*	-15.0*
UUI episodes/24 h						
Baseline	3.7	3.8	3.7	3.7	3.9	3.9
Mean change	-1.14	-1.95*	-2.22*	-0.96	-1.65*	-2.28*
Median % change		-80.0*	-87.5*		-67.4*	-81.8*
MVV/mL						
Baseline mean	150.2	160.0	153.9	159	152	156
Mean change	9.37	27.72*	33.62*	8.38	16.5	33.6*
Urgency episodes/24 h						
Baseline	11.4	11.0	11.5	11.4	12.5	11.6
Mean change	-1.07	-1.88*	-2.36*	-0.79	-1.91*	-2.30*
Median % change	-11.1	-17.6*	-19.1*	-3.3	-16.3*	-18.4*
Continent days/wk						
Baseline mean	0.8	0.8	0.6	0.6	0.7	0.7
Mean change	2.07	2.84*	3.32*	1.31	2.33*	2.80*

*Statistically significant compared to placebo.

Abbreviations: MVV, mean volume voided; UUI, urgent urinary incontinence.

Fesoterodine 8 mg vs tolterodine ER 4 mg

A post-hoc inferential analysis was conducted on the primary endpoint (micturitions/24 hours), the two co-primary endpoints (UUI episodes/24 hours and treatment response), several secondary endpoints (including continent days per week and mean volume voided) comparing patients receiving fesoterodine 8 mg and tolterodine ER 4 mg in the phase III European trial. Fesoterodine 8 mg was statistically significantly better than tolterodine ER 4 mg for improving urgency UUI episodes, mean volume voided and number of continent days per week.³⁵

Fesoterodine 4 mg vs fesoterodine 8 mg

A pooled analysis of the data from the 2 phase III clinical trials for patients receiving fesoterodine 4 mg, fesoterodine 8 mg and placebo was performed. At the end of treatment, both doses of fesoterodine showed statistically significant improvements in all efficacy endpoints vs placebo ($P < 0.01$). These effects were seen 2 weeks after initiation of treatment (the earliest evaluation point) and were sustained throughout the treatment period. Fesoterodine 8 mg performed significantly better than fesoterodine 4 mg in improving all diary variables ($P < 0.05$) except micturition frequency, demonstrating a dose-response relationship.³⁶

Tolerability and safety of fesoterodine

The safety and tolerability of fesoterodine have been evaluated in phase II and III controlled trials involving 2859 OAB patients, of which 2288 were treated with fesoterodine. Approximately 80% of these individuals were treated with fesoterodine for >10 weeks. In these studies, the incidence of serious adverse events in patients receiving placebo fesoterodine 4 mg and fesoterodine 8 mg were 1.9%, 3.5% and 2.9%, respectively. In only 4 patients receiving fesoterodine were the serious adverse events felt to be related or likely due to study medication. Each of these 4 patients had 1 reported serious adverse event: angina, chest pain, and gastroenteritis, and QT prolongation on ECG.

The most commonly reported adverse event in patients treated with fesoterodine, was dry mouth, a commonly reported side effect of antimuscarinic therapy. The incidence of dry mouth varied from 19% for those taking fesoterodine 4 mg to 35% taking fesoterodine in the fixed dose studies, compared to 7% for placebo. In most cases, the dry mouth was mild or moderate and discontinuations related to dry mouth were 0.4%, 0.4% and 0.8% in patients receiving placebo, fesoterodine 4 mg and fesoterodine 8 mg, respectively.

Constipation was reported in 2% of subjects taking placebo, 4% in those taking fesoterodine 4 mg and 6% in those taking 8 mg of fesoterodine. Dry eyes were reported in 0% patients taking placebo, 1.4% on fesoterodine 4 mg and 3.7% taking fesoterodine 8 mg.²⁰

Three-year open-label extension trials after 1 phase II and both phase III controlled trials demonstrated similar adverse events as reported in the 12-week, placebo-controlled studies. As with the controlled trials, most cases of dry mouth and constipation were mild to moderate in intensity. Serious adverse events deemed to be at least possibly related to study medication by the investigator and reported more than once in the open-label treatment period of up to 3 years included urinary retention (3 cases), diverticulitis (3 cases), constipation (2 cases), irritable bowel syndrome (2 cases) and electrocardiogram QT corrected interval prolongation (2 cases).²⁰

Effects on QT interval

A double-blind, placebo-controlled, parallel-group study involving 261 healthy subjects was performed to assess effects of fesoterodine on the QT interval. Individuals received fesoterodine 4 mg or 28 mg, placebo or moxifloxacin (a positive control). There was no effect of fesoterodine on the QT interval at the 4 mg dose or 28 mg dose. Additional assessments of the QT interval in other fesoterodine clinical trials did not show any increase in the QT interval.²⁰

Heart rate

In the two phase III trials, the mean increase in heart rate compared to placebo was approximately 3 to 4 beats per minute in the 4 mg/day group and 3 to 5 beats per minute in the 8 mg/day group.²⁰

Contraindications and precautions

As with all antimuscarinic agents approved for the use of OAB, fesoterodine is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma. It is also contraindicated in patients with a known hypersensitivity to the drug or its metabolites. Fesoterodine should be used with caution in patients with clinically significant bladder outlet obstruction, decreased gastrointestinal motility, patients with controlled narrow-angle glaucoma and patients with myasthenia gravis.

In patients with mild to moderate hepatic impairment, there is no need to adjust the dose of fesoterodine. However, as it has not been studied in patients with severe hepatic impairment its use is not recommended in this

patient population. In individuals with mild or moderate renal insufficiency there is no dosage adjustment required, however, doses greater than 4 mg are not recommended in patients with severe renal insufficiency.

Doses of fesoterodine greater than 4 mg are not recommended in patients taking potent CYP3A4 inhibitors such as ketoconazole, itraconazole and clarithromycin. In patients taking weak or moderate CYP3A4 inhibitors such as erythromycin, careful assessment of tolerability at the 4 mg daily dose is recommended before increasing to 8 mg.

When used in conjunction with other antimuscarinics, the antimuscarinic side effects may be potentiated. Anticholinergic agents can potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility.²⁰

There is no dosage adjustment recommended for age, gender or race.

Patient-reported outcomes

OAB is a condition which has a significant impact on quality of life. Although assessment of voiding diary parameters, particularly volume voided, provide objective measures of treatment response, it is the patient's perception of treatment benefit and the effects on his/her quality of life that often impacts on whether or not a patient will continue with therapy. Each patient may have individual treatment expectations and thus when evaluating and managing patient's with OAB it is important to identify the patient's treatment expectations to ensure they are realistic and to identify such factors which will govern their assessment of response to therapy.

US phase III clinical trial – patient reported outcomes

The King's Health questionnaire (KHQ), the international consultation of incontinence questionnaire, short-form (ICIQ-SF) and a Likert scale assessment of bladder-related problems were completed by patients at baseline and at week 12 of treatment. The KHQ is a validated disease specific quality of life questionnaire assessing QOL in women with urinary incontinence. It comprises 21 items divided into 9 domains: severity (coping), emotions, role limitations, physical limitations, social limitations, sleep/energy, personal relationship, impact on life and general health.^{37,38} Both active arms in the study (fesoterodine 4 mg and 8 mg) demonstrated greater improvements in subjects' quality of life compared to placebo. The 8 mg dose of fesoterodine produced significantly greater improvement over placebo in 7 of the 9 KHQ domains ($P < 0.05$; all domains except general health

and personal relationships). Fesoterodine 4 mg produced significantly greater improvement compared to placebo on 2 out of 9 KHQ domains. The ICIQ-SF is a validated incontinence-specific quality of life questionnaire that consists of 3 scored items (the frequency of leakages, usual amounts of leakages and the impact on daily life). The total score is a sum of the 3 scored items yielding a score ranging from 0 to 21, with higher scores indicating more significant incontinence and impact.³⁹ Both doses of fesoterodine produced significantly greater improvements compared to placebo on ICIQ-SF scores ($P < 0.0025$). In addition, the proportion of subjects reporting improvement in their bladder-related problems on the Likert scale was statistically significantly greater than placebo in both fesoterodine arms, 4 mg ($P = 0.0175$) and 8 mg ($P = 0.0005$), based on the 3-category analysis of the changes from baseline (improvement, no change, or deterioration). There was a 54.5% and 62.3% improvement in the Likert scale with fesoterodine 4 mg and 8 mg, respectively, compared to 46% with placebo.⁴⁰

Pooled data from the two phase III clinical trials

Pooled data from two randomized placebo-controlled phase III studies were analyzed. Eligible patients with frequency and urgency or urgency urinary incontinence were randomized to placebo or fesoterodine 4 or 8 mg for 12 weeks; one trial also included tolterodine ER 4 mg. HRQoL was assessed using the KHQ, ICIQ-SF, a six-point Likert scale measuring the severity of bladder-related problems, and treatment response.

By the end of treatment, all active-treatment groups had significantly improved HRQoL compared with those on placebo, as shown by an improvement in the KHQ and ICIQ-SF scores, treatment response rate, and a major improvement in self-reported bladder-related problems. The fesoterodine 8-mg group had statistically significant improvements over placebo in 8 of 9 KHQ domains. Fesoterodine 4 mg and tolterodine ER produced statistically significant improvements in 7 of 9 KHQ domains compared to placebo. Fesoterodine 8 mg gave better results than 4 mg in 2 domains; Emotions and Symptom Severity ($P < 0.05$). A major improvement (≥ 2 points) in bladder-related problems was reported by 33% of patients on fesoterodine 4 mg, 38% on fesoterodine 8 mg, and 34% on tolterodine ER, vs 21% on placebo ($P < 0.001$).⁴¹

Effects of flexible dose fesoterodine on treatment satisfaction and quality of life were evaluated in a 12-week, multi-center, open-label, single arm, flexible dose study.⁴²

Five hundred and sixteen subjects participated in the study and started on 4 mg of fesoterodine. At week 4 they could either continue on 4 mg of fesoterodine or increase to 8 mg of fesoterodine. Patient treatment satisfaction and quality of life were assessed with the treatment satisfaction questionnaire, the patient perception of bladder condition (PPBC) and the OAB questionnaire (OAB-q). The PPBC is a single item, 6 point instrument used by subjects to rate severity of their bladder related problems, ranging from my bladder causes me no to many severe problems.⁴³ The OAB-q is an 8 item symptom bother scale and a 25-item health related quality of life scale with 4 domains (concern, coping, sleep and social interaction).³⁹ Approximately 50% of the subjects opted to dose escalate at week 4. Approximately 80% of the subjects who responded to the treatment satisfaction question at week 12 reported satisfaction with treatment, 38% being very satisfied. Using the PPBC, 83% of subjects reported improvement at week 12 with 59% reporting improvements of ≥ 2 points. Significant improvements from baseline were noted in OAB-q symptom bother and health related quality of life scales and all 4 health related quality of life domains.⁴²

Conclusions

Overactive bladder is a highly prevalent condition associated with significant impact on quality of life, associated morbidities and cost. Antimuscarinic agents remain one of the first line therapies for treatment. Use of antimuscarinic agents in combination with behavioral therapy is more effective than either therapy used alone. Fesoterodine is the newest antimuscarinic agent approved for the treatment of OAB. In addition to the statistically significant improvements seen in voiding diary parameters with both 4 mg and 8 mg of fesoterodine compared to placebo, a dose-dependent response was noted between 4 mg and 8 mg of fesoterodine. This dose response has not been demonstrated with all of the other antimuscarinic agents that offer multiple doses. Only oxybutynin has shown statistically significant differences between the 15 mg dose and the 2 lower doses (5 mg, 10 mg) for reduction of urgency urinary incontinence episodes and mean volume voided per micturition.⁴⁴ Dose separation has not been demonstrated for efficacy outcomes with darifenacin^{45,46} solifenacin⁴⁷ and tolterodine^{48,50} Both doses of fesoterodine have demonstrated significant improvements in patients' perception of treatment outcomes as reflected by the treatment response questionnaire and the PPBC. In addition, statistically significant improvements in HRQoL have been demonstrated for both doses using the KHQ and the OAB-q. The improvements in OAB symptoms and quality of life are complemented by its favorable

tolerability and safety profile. Dry mouth, the most common side effect, tends to be mild to moderate in nature and led to few discontinuations in clinical trials. There are relatively few situations in which fesoterodine is not recommended or in which require dosage limitations are recommended.

Despite the number of antimuscarinic therapies available to patients and the ability to try alternative antimuscarinic therapies, some patients will ultimately fail antimuscarinic therapy. Neuromodulation via a surgically implanted device (Interstim, Medtronic) or via percutaneous routes (percutaneous tibial nerve stimulation) are approved options for the management of OAB and are typically employed as second-line therapies. Injection of botulinum toxin into the detrusor for the treatment of OAB remains investigational. A greater understanding of the role of the urothelium and suburothelium and the central nervous system and their possible roles in OAB symptoms has prompted investigation of agents that may modulate the afferent pathway and central nervous system pathways of OAB.

Disclosure

Dr. Ellsworth is a consultant and speaker for Pfizer, and a consultant, speaker and study investigator for Novartis.

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