



CDEC FINAL RECOMMENDATION

FESOTERODINE FUMARATE EXTENDED-RELEASE

(Toviaz – Pfizer Canada Inc.)

Indication: Bladder, Overactive

Recommendation:

The Canadian Drug Expert Committee (CDEC) recommends that fesoterodine be listed in a similar manner to extended-release tolterodine.

Reasons for the Recommendation:

1. In three double-blind, randomized controlled trials (RCTs) in patients with overactive bladder, compared with extended-release tolterodine, fesoterodine produced similar reductions in daily urinary urge incontinence and micturition events.
2. At the submitted price, the daily cost of fesoterodine (4 mg to 8 mg daily, [*confidential price removed at manufacturer's request*]) is less expensive than extended-release tolterodine (4 mg daily, \$1.91). The confidential price was used by the Committee in making the listing recommendation and the manufacturer requested that this information be kept confidential pursuant to the CDR Confidentiality Guidelines.

Background:

Fesoterodine fumarate extended-release has a Health Canada indication for the treatment of patients with overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence, or any combination of these symptoms. Fesoterodine fumarate is an anticholinergic antispasmodic agent. It is available in 4 mg and 8 mg extended-release tablets. The starting dose approved by Health Canada is 4 mg once daily; based on individual response and tolerability the dose may be increased to 8 mg once daily.

Summary of CDEC Considerations:

The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of double blind RCTs, and a critique of the manufacturer's pharmaco-economic evaluation. No patient groups responded to the CDR Call for Patient Input. The manufacturer submitted a confidential price for fesoterodine.

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Clinical Trials

The systematic review included three 12-week multinational, double-blind RCTs of patients with a history of overactive bladder, with symptoms of urinary frequency, urgency, or urge incontinence. Of patients included in the three trials, 57% had not previously failed treatment with another overactive bladder medication, and the proportion of patients failing treatment with oxybutynin is unknown.

- Study SP583 (N = 1,135) randomized patients to one of four treatment groups: fesoterodine (4 mg or 8 mg daily), extended-release tolterodine 4 mg daily, or placebo.
- Studies A0221008 (N = 1,712) and A221046 (N = 2,417) randomized patients to one of three treatment groups: fesoterodine 4 mg daily for one week followed by 8 mg once daily for the remaining 11 weeks, extended-release tolterodine 4 mg daily, or placebo.

The frequency of premature treatment discontinuation was 13.0%, 9.8%, and 9.6% in studies SP583, A0221008, and A221046 respectively, with no notable differences between treatments.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: change in the number of (i) urge incontinence episodes, (ii) micturition events, (iii) nocturia events; quality of life; serious adverse events; total adverse events; and withdrawal due to adverse events. The co-primary outcomes in study SP583 included both the 12-week change from baseline in the average number of micturition and urinary urge incontinence episodes per 24 hours, and treatment response. The primary outcome in studies A0221008 and A0221046 was the 12-week change from baseline in the average number of urinary urge incontinence episodes per 24 hours.

Quality of life was assessed using the King's Health Questionnaire (KHQ) in trial SP583 and the Overactive Bladder Questionnaire (OAB-q) in trials A0221008 and A0221046. The OAB-q is a 33-item questionnaire that assesses how much the subject has been bothered by bladder symptoms during the previous week. The total score ranges from 33 to 198 (1 to 6 for each item); higher scores reflect worsening impact. The King's Health Questionnaire includes 32 items that measure general health perception, incontinence impact, severity of urinary symptoms, and seven domains: role limitations, physical limitations, social limitations, personal relationships, emotions, sleep and energy, and severity (coping) measures. Scores range from 0 (best) to 100 (worst).

Results

Efficacy or Effectiveness

- Compared with extended-release tolterodine, patients treated with fesoterodine 8 mg daily reported a statistically significant greater reduction in the number of urinary urge incontinence episodes per day; the respective mean differences (MD) (95% confidence interval [CI]) in studies SP583, A0221008, and A0221046 were -0.48 (-0.92 to -0.05), -0.11 (-0.2 to -0.02), and -0.21 (-0.36 to -0.06). The reduction in the number of urinary urge incontinence episodes was not statistically significantly different between fesoterodine 4 mg and tolterodine.

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- The reduction in the number of micturition events per day was not statistically different between tolterodine and fesoterodine treatment groups in studies SP583 and A0221008. In study A0221046, patients treated with fesoterodine 8 mg reported a statistically significant greater reduction in micturition events compared with tolterodine; MD (95% CI): -0.4 (-0.6 to -0.1).
- The reduction in the number of nocturia events was not statistically significantly different between tolterodine and fesoterodine treatment groups in the reviewed trials.
- Compared with tolterodine, fesoterodine-treated patients reported a statistically significant greater improvement in quality of life as assessed by the OAB-q total score in studies A0221008 and A0221046. Improvement in quality of life, when assessed by the KHQ in study SP583, was not statistically significantly different between fesoterodine and tolterodine.

Harms (Safety and Tolerability)

- The proportion of patients experiencing serious adverse events was not statistically significantly different between tolterodine and fesoterodine treatment groups in any of the reviewed trials.
- The proportion of patients reporting an adverse event was statistically significantly higher in the fesoterodine 8 mg groups (58%, 52.0%, and 47.8%) compared with tolterodine (50%, 40.9%, and 38.5%) in studies SP583, A0221008, and A0221046, respectively. Compared with tolterodine, fesoterodine 8 mg was associated with a statistically significant higher incidence of dry mouth and constipation in three studies and two studies respectively.
- The incidence of withdrawal due to adverse events was statistically significantly higher for fesoterodine 8 mg compared with tolterodine in study A0221046; the incidence of withdrawal due to adverse events was not statistically significantly different between the tolterodine and fesoterodine groups in studies SP583 and A0221008.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis comparing fesoterodine with other oral therapies approved for overactive bladder (tolterodine, solifenacin, trospium, and darifenacin) based on clinical trial information (SP583, A0221008, A0221046) for clinical efficacy and a published network meta-analysis for adverse events. CDR noted that, based on the evidence from the clinical trials, the incidence of overall adverse events was higher with fesoterodine 8 mg than tolterodine, which may not support the assumption of similar safety for fesoterodine at the 8 mg dose.

At the submitted confidential price, the daily cost of fesoterodine (4 mg to 8 mg, [confidential price removed at manufacturer's request]) is less expensive than extended-release tolterodine (4 mg daily, \$1.91), solifenacin (5 mg to 10 mg daily, \$1.64), trospium (20 mg twice daily, \$1.55), darifenacin (7.5 mg to 15 mg daily, \$1.58), extended-release oxybutynin (5 mg to 30 mg daily, \$1.83 to \$5.50); but it is more expensive than immediate-release oxybutynin (5 mg two to four times daily, \$0.20 to \$0.39).

Patient Input Information:

No patient groups responded to the CDR Call for Patient Input.

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Other Discussion Points:

- The Committee noted that central nervous system (CNS) adverse effects of anticholinergic agents are of particular concern in the elderly. The Committee discussed that, while the reviewed trials did not report between-treatment differences in CNS adverse events, such events may be poorly characterized in clinical trials.

CDEC Members:

Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Julia Lowe, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

September 19, 2012 Meeting**Regrets:**

Two CDEC members did not attend.

Conflicts of Interest:

None

About this Document:

CDEC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC made its recommendation. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The Final CDEC Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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