

**fesoterodine fumarate 4mg and 8mg prolonged release tablets  
(Toviaz<sup>®</sup>)**

**No. (480/08)**

**Pfizer Ltd**

06 June 2008

The Scottish Medicines Consortium has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

**fesoterodine fumarate** prolonged release tablets (**Toviaz<sup>®</sup>**) are accepted for restricted use within NHS Scotland for treatment of the symptoms (increased urinary frequency and/or urgency and/or urgency incontinence) that may occur in patients with overactive bladder syndrome.

Fesoterodine is effective in reducing symptoms associated with overactive bladder syndrome without a neurological cause and was of equivalent efficacy to a comparator antimuscarinic agent in one study.

Fesoterodine is associated with adverse effects typical of antimuscarinic agents used in this condition. It is restricted to second-line use as there are cheaper antimuscarinics available that would normally be used as first-line agents.

Overleaf is the detailed advice on this product.

**Chairman,  
Scottish Medicines Consortium**

**Indication**

Treatment of the symptoms (increased urinary frequency and/or urgency and/or urgency incontinence) that may occur in patients with overactive bladder syndrome.

**Dosing information**

For adults, (including the elderly), the recommended starting dose is 4mg once daily, swallowed whole with liquid. Based upon individual response, the dose may be increased to a maximum of 8mg once daily. Efficacy should be evaluated after 8 weeks.

**Product availability date**

Estimated June 2008

**Summary of evidence on comparative efficacy**

Overactive bladder (OAB) syndrome describes a complex of lower urinary tract symptoms, (including urinary urgency, with or without urge incontinence, and usually frequency and nocturia), that occur in the absence of pathologic or metabolic causative factors. OAB includes patients with and without a possible neurological cause for their symptoms.

Fesoterodine is a competitive, specific and non-selective muscarinic receptor antagonist formulated as a prolonged release tablet. It acts as a pro-drug after oral administration with rapid and extensive hydrolysis to the same active metabolite as tolterodine. The submitting company has indicated that it expects fesoterodine to be used as a second-line treatment if patients fail to respond to, or tolerate, non-proprietary immediate-release oxybutynin.

There were two pivotal studies of similar design. Both were double-blind, placebo-controlled multicentre studies employing two doses of fesoterodine prolonged release. One study had an active comparator (tolterodine extended release (ER) but was not powered to detect a difference between fesoterodine and tolterodine ER. Both studies included patients aged  $\geq 18$  years with a medical history of OAB symptoms, who had urinary urgency for  $\geq 6$  months,  $\geq 8$  micturitions/24 h, either  $\geq 6$  urgency episodes or  $\geq 3$  urge urinary incontinence (UUI) episodes during a 3-day diary period and who had indicated on a Likert scale that they had at least moderate OAB problems. Patients were excluded if there was a neurological cause for the OAB.

The primary outcome was change in the average number of micturitions/24 hours. The primary analysis used analysis of covariance with treatment and region as factors and baseline value as covariate. The full analysis set (FAS) was defined as all randomised patients who received any study medication, and for whom baseline and double-blind micturition data were available. Missing data were imputed using last observation carried forward (LOCF). The co-primary outcome was patient-reported treatment response (yes/no variable), measured on a treatment benefit scale, where 1 = greatly improved (yes), 2 = improved (yes), 3 = unchanged (no), and 4 = worsened (no). Patients completed a 3-day diary during the placebo run-in phase and on the days immediately preceding three subsequent visits.

Patients, 1135 in the active-controlled study and 836 in the placebo-controlled study were randomised equally to once daily treatment with fesoterodine 4mg, fesoterodine 8mg, placebo or, (active-controlled trial only), tolterodine ER 4mg, for 12 weeks. Over both trials, the mean age was 56 to 59 years, >75% were female and most were Caucasian, 98% and 82%, in the active and placebo-controlled studies respectively.

In both studies all active treatments significantly improved the primary outcome of micturitions/24hours compared with placebo. In each study baseline micturition frequency was approximately 12/24 hours. In the active-controlled study, compared to placebo, the treatment difference (95% confidence interval (CI)) was -0.8 (-1.26 to -0.36), -0.9 (-1.38 to -0.49), -0.8 (-1.23 to -0.34) for fesoterodine 4mg, fesoterodine 8mg and tolterodine ER 4mg, respectively. In the placebo-controlled study, the treatment difference (95% CI) was -0.5 (-1.02 to -0.04) and -1.0 (-1.50 to -0.52) for fesoterodine 4mg and fesoterodine 8mg respectively.

Patient-reported treatment response was 75%, 79%, 72% and 53% in patients receiving fesoterodine 4mg, fesoterodine 8mg, tolterodine ER 4mg and placebo, respectively in the active-controlled study, and 64%, 74% and 45% for fesoterodine 4mg, 8mg and placebo, respectively, in the placebo-controlled study.

In the active-controlled study, all three active treatments were significantly better than placebo for the secondary variables of reduction in UUI episodes/24 hours, daytime micturitions and urgency episodes. Fesoterodine 4mg and 8mg but not tolterodine ER 4mg produced significant reductions compared to placebo in continent days per week. There was no difference between treatment groups in change in nocturnal micturitions. In the placebo-controlled study the secondary outcome of UUI/24 hours was significantly improved compared to placebo by 0.7 and 1.3 with fesoterodine 4mg and 8mg respectively.

Quality of life assessed by the disease specific, nine domain King's Health Questionnaire found significant improvements over placebo with fesoterodine 4mg in six and two domains, and with fesoterodine 8mg in eight and seven domains for the active and placebo-controlled studies, respectively.

The International Consultation on Incontinence Questionnaire - Short Form (ICIQ-SF), used to assess the impact of bladder problems, has a score of 0 (low bother) to 21 (maximum bother). There were small but significant improvements on the ICIQ-SF compared with placebo for all active treatments. Mean changes after 12 weeks were 4.4, 4.4, 4.0 and 2.6 for fesoterodine 4mg, fesoterodine 8mg, tolterodine ER 4mg and placebo, respectively.

## **Summary of evidence on comparative safety**

The safety profile of fesoterodine is compatible with its antimuscarinic activity. No major safety concerns have been identified.

In the active comparator study, adverse events (AEs) occurred in 58% of patients in the fesoterodine 8mg group and in 50% of patients in both the fesoterodine 4mg and tolterodine ER 4mg groups. The most frequent AE in all treatment groups was dry mouth, which was mild or moderate in most cases, but reported as being severe in 3% of patients taking fesoterodine 8mg, who reported severe dry mouth.

Most AEs were mild in intensity. Severe AEs were experienced by 2% of patients receiving placebo, 3% receiving fesoterodine 4mg, 8% receiving fesoterodine 8mg, and 3% receiving tolterodine ER 4mg. With the exception of dry mouth, no AE occurred in more than 5% of patients.

## **Summary of clinical effectiveness issues**

The pivotal studies had several limitations. The only study with an active comparator, (tolterodine ER), was not powered to detect a statistical difference between fesoterodine and the comparator. In addition this study had a 13% dropout rate, which may have reduced its intended power. Although post hoc analyses were conducted, no data concerning primary outcomes were provided.

In both studies the treatment benefits produced by fesoterodine were modest. Patients in the pivotal studies recorded events in diaries over 3-day periods. EMEA guidance recommends that diaries are recorded over a week.

The term overactive bladder includes those patients with a possible neurological cause for their symptoms. The pivotal studies excluded patients with OAB due to neurological disease; therefore the efficacy of fesoterodine in this patient group is unknown.

Patients in the active comparator study had a mean age of 56 to 58 years, approximately 80% were female and 98% were Caucasian. This may not represent the OAB patient population in Scotland, especially with respect to age.

The pivotal studies were only of 12 weeks duration. Although supportive open label extension studies are ongoing, it is difficult to draw conclusions on efficacy from interim results, due to the lack of control and the high number of drop-outs. At the time of the data cut-off only 665 out of 1144 patients enrolled in open label treatment remained.

The submitting company has indicated that it expects fesoterodine would usually be used as a second-line treatment after patients have failed to respond to or tolerate non-proprietary immediate-release oxybutynin. However, no evidence has been presented to demonstrate efficacy of fesoterodine in this refractory patient group.

## **Summary of comparative health economic evidence**

The manufacturer submitted a cost-minimisation analysis comparing fesoterodine to tolterodine ER. The manufacturer sought a position for fesoterodine as a treatment option for patients refractory to, or intolerant of, generic oxybutynin. The main analysis presented by the manufacturer relied upon the results of the trial which had 4mg tolterodine ER as the active comparator. The limitations of this evidence base are noted in the previous section but from this, the manufacturer concluded that fesoterodine was at least clinically equivalent to 4mg tolterodine ER. Since 4mg and 8mg fesoterodine are the same price as 4mg tolterodine ER, the manufacturer concluded that fesoterodine would be at least as cost effective as 4mg tolterodine ER. It should be noted that other possible comparators such as darifenacin were not considered, despite being of lower cost than fesoterodine.

The direct drug cost comparison with tolterodine ER was augmented with non-drug cost savings that the manufacturer suggested might arise from the use of 8mg fesoterodine as compared with 4mg tolterodine ER, based upon the results of the active-controlled trial. This was a relatively simple model and did not anticipate patients with uncontrolled symptoms switching to other treatments. It did not formally demonstrate that general use of fesoterodine, which is available as both 4mg and 8mg, would result in cost savings.

## **Summary of patient and public involvement**

A Patient Interest Group submission was not made.

## **Additional information: guidelines and protocols**

In October 2006, the National Institute for Health and Clinical Excellence (NICE) published a guideline on the management of urinary incontinence (UI) in women. It notes that there is no evidence of a clinically important difference in efficacy between antimuscarinic drugs. If bladder training is ineffective, it recommends the use of immediate release (IR) non-proprietary oxybutynin as the most cost-effective option in women with OAB or mixed UI. If not tolerated, alternatives are darifenacin, solifenacin, tolterodine, trospium or other formulations of oxybutynin. Propiverine should be considered as an option to treat frequency of urination in women with OAB, but is not recommended for the treatment of UI. Flavoxate, propantheline and imipramine should not be used for the treatment of UI or OAB in women.

In December 2004, the Scottish Intercollegiate Guidelines Network (SIGN) published a national clinical guideline on management of urinary incontinence in primary care. It recommended that a trial of oxybutynin, propiverine, tolterodine or trospium be given to patients with significant urgency with or without urge incontinence. The dose should be titrated to combat adverse effects. Antimuscarinic therapy should be tried for a period of six weeks to enable an assessment of the benefits and side-effects. Treatment should be reviewed after six months to ascertain continuing need.

In March 2005, the European Association of Urology published guidelines on urinary incontinence recommending the use of antimuscarinic drugs specific circumstances but without referring to individual drugs.

## **Additional information: previous SMC advice**

After review of a full submission, SMC issued advice in June 2007 that darifenacin (Emselex®) is accepted for restricted use within NHS Scotland for the symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder syndrome. Darifenacin is effective in reducing symptoms associated with overactive bladder, including frequency, urgency and incontinence and the treatment effect is similar to another antimuscarinic. Darifenacin is associated with adverse effects typical of antimuscarinic agents used in this condition. It is restricted to second line use as there are cheaper antimuscarinics available that would normally be used as first-line agents.

After review of a resubmission, SMC issued advice in November 2005 that solifenacin succinate (Vesicare®) is accepted for use within NHS Scotland for the symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with

overactive bladder syndrome. Solifenacin is effective in reducing symptoms associated with overactive bladder, including frequency, urgency and incontinence. It is associated with adverse events typical of antimuscarinic agents used in this condition. There are cheaper antimuscarinics available that would normally be used as first-line agents.

After review of a full submission, SMC issued advice in August 2005 that oxybutynin transdermal patch (Kentera®) is accepted for restricted use within NHS Scotland for the treatment of urge incontinence and/or increased urinary frequency and urgency in patients with unstable bladder, restricted to patients who derive clinical benefit from oral oxybutynin but who experience intolerable anticholinergic side effects. It should be used in conjunction with non-pharmacological measures, including pelvic floor muscle exercises and bladder retraining. Transdermal oxybutynin appears to have similar efficacy to oral antimuscarinics and a lower rate of anticholinergic adverse events. However, patients have the additional effect of application site reactions, which in some patients lead to treatment discontinuation. Transdermal oxybutynin has a lower total cost than oral tolterodine, but a higher total cost than oral oxybutynin.

After review of an abbreviated submission, SMC issued advice in February 2007 that propiverine hydrochloride 30 mg modified release capsule (Detrunorm XL®) is accepted for use in NHS Scotland for the treatment of urinary incontinence, as well as urgency and frequency in patients who have idiopathic detrusor overactivity (overactive bladder). For patients for whom propiverine is appropriate it allows once-daily dosing, compared to twice daily dosing with an existing solid oral dose formulation, at no increased cost.

### Additional information: comparators

The main comparators are other antimuscarinic drugs: oxybutynin, tolterodine, solifenacin darifenacin and trospium. Pelvic floor muscle exercise and bladder training are also recommended for OAB.

### Cost of relevant comparators

Drug	Dose regimen	Cost per year (£)
<b>fesoterodine prolonged release</b>	<b>4 to 8mg daily</b>	<b>377</b>
oxybutynin prolonged release tablets	5 to 20mg daily	139 to 557
solifenacin	5 to 10mg daily	335 to 436
tolterodine immediate release tablets	2mg twice daily	397
tolterodine prolonged release capsules	4mg daily	377
oxybutynin patch	One patch twice weekly	354
darifenacin	7.5 to 15mg daily	340
trospium	20mg twice daily	315
oxybutynin immediate release tablets	2.5mg twice daily (initial dose in elderly) to 5mg four times daily	51 to 59

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 27.03.08.

### **Additional information: budget impact**

Given market shares, the price parity between fesoterodine and tolterodine ER and the likelihood of fesoterodine mainly displacing tolterodine ER (the market leader), the manufacturer estimated that the overall budget impact of introducing fesoterodine in Scotland would be negligible.

**Advice context:**

*No part of this advice may be used without the whole of the advice being quoted in full.*

*This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.*

*This assessment is based on data submitted by the applicant company up to and including 15 May 2008.*

*Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.*

*The undernoted references were supplied with the submission. Those shaded grey are additional to those supplied with the submission.*

Chapple C, Van KP, Tubaro A, Haag-Molkenteller C, Forst HT, Massow U, et al. Clinical efficacy, safety, and tolerability of once-daily fesoterodine in subjects with overactive bladder. *Eur Urol* 2007 October;52(4):1204-12.

Nitti VW, Dmochowski R, Sand PK, Forst HT, Haag-Molkenteller C, Massow U, et al. Efficacy, safety and tolerability of fesoterodine for overactive bladder syndrome. *J Urol* 2007 Dec;178(6):2488-94.

Pfizer. SP583 clinical study report. Data on file.

Pfizer. SP584 clinical study report. Data on file.

The European Medicines Agency (EMA) European Public Assessment Report. Fesoterodine fumarate prolonged release tablets (Toviaz®).2007 EMA H-C-723. ([www.emea.europa.eu/humandocs/Humans/EPAR/toviaz](http://www.emea.europa.eu/humandocs/Humans/EPAR/toviaz)).

The European Medicines Agency (EMA) Committee for Proprietary Medicinal Products Note for guidance on the clinical investigation of medicinal products for the treatment of urinary incontinence. 18<sup>th</sup> December 2002 CPMP/EWP/18/01/final ([www.emea.europa.eu](http://www.emea.europa.eu)).