#147

**Benefit-Risk Evaluation of Tolterodine 4 mg and Fesoterodine Fixed and Flexible Dosing**

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## 1 Introduction

- Clinicians use the most recent available clinical data to select and optimise treatment options for overactive bladder (OAB). These data are often driven by safety or efficacy, with limited published benefit-risk (BR) assessments available. Fragmented data can cause difficulty in quantifying the BR profile of medicines, leading to challenges in clinical decision making.
- Simple tools are needed to ascertain the BR of individual medicines. This is of specific concern for clinicians selecting an OAB treatment because several options are available with differing mechanisms of action and efficacy and safety profiles.8
- Computer-based models may be used to assess BR profiles.4,7,8 These models combine the best available evidence with clinical judgement about the data to provide valid and reliable decision-making guides.
- A multicriteria decision analysis (MCDA) computer-based model assessed the BR profiles of 12 OAB drug-treatment options; 3 profiles associated with fesoterodine (FES) and tolterodine (TOL) are reported here.

## 2 Methods

- Efficacy and safety data from published, randomised, placebo (PBO)-controlled trials of TOL and FES were used to populate an MCDA model.
- Using European Medicines Agency–accepted methodology, data were evaluated against the 4 symptomatic benefits and 7 unfavourable effects judged most likely to affect patient outcomes (Figure 1).
- TOL 4 mg and FES 4- and 8-mg fixed doses and a FES flexible-dosing regimen (4 or 8 mg) were analysed.
- Using available clinical evidence or assessment, each criterion was scored from 0 to 100 (ie, closest preferred to most preferred data points) for the full model. Values in between those points were assigned relative values in the same relative positions as given by the data.
- Data were weighted in the full model by (i) relative weighting of the criteria for symptomatic benefit criteria, (ii) relative weighting comparing swings for symptomatic benefit criteria, and (iii) relative weighting of highest-weighted symptomatic benefit criterion against highest-weighted unfavourable effect criterion.
- Sensitivity analyses were performed by varying the criteria weighting to determine if overall results were affected.
- Data are quantitative; no statistical comparisons were made.

## 3 Results

### Comparison of BR profiles

- The model showed a favourable BR profile for FES flexible dosing compared with TOL and FES single-dose interventions (Figure 2).

### Figure 2. Overall BR Profile of TOL 4 mg, FES 4 mg, and FES Flexible Dosing (4 or 8 mg) by Individual Symptomatic Benefit and Unfavourable Effect Criteria

<table>
<thead>
<tr>
<th>Symptomatic Benefit</th>
<th>Overall BR</th>
<th>Symptomatic Benefit</th>
<th>Overall BR</th>
<th>Symptomatic Benefit</th>
<th>Overall BR</th>
<th>Symptomatic Benefit</th>
<th>Overall BR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urgency/UII</td>
<td>26.9</td>
<td>21.5</td>
<td>10.8</td>
<td>4.6</td>
<td>2.2</td>
<td>0.5</td>
<td>0.3</td>
</tr>
<tr>
<td>Frequency</td>
<td>90.8</td>
<td>85.6</td>
<td>72.4</td>
<td>52.9</td>
<td>41.5</td>
<td>34.3</td>
<td>31.6</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>24.0</td>
<td>26.9</td>
<td>24.0</td>
<td>24.0</td>
<td>11.0</td>
<td>21.2</td>
<td>21.2</td>
</tr>
<tr>
<td>Constipation/Headache</td>
<td>5.9</td>
<td>9.0</td>
<td>7.1</td>
<td>8.6</td>
<td>1.0</td>
<td>0.5</td>
<td>0.7</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2.2</td>
<td>22.2</td>
<td>10.8</td>
<td>16.1</td>
<td>8.6</td>
<td>26.9</td>
<td>26.9</td>
</tr>
<tr>
<td>Retention</td>
<td>0.5</td>
<td>0.0</td>
<td>0.5</td>
<td>0.5</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>0.6</td>
<td>10.8</td>
<td>1.1</td>
<td>0.3</td>
<td>2.6</td>
<td>4.6</td>
<td>4.6</td>
</tr>
</tbody>
</table>

### Overall BR Profile of TOL 4 mg, FES 4 mg, and FES Flexible Dosing (4 or 8 mg) and PBO

<table>
<thead>
<tr>
<th>Overall BR</th>
<th>Symptomatic Benefit</th>
<th>Overall BR</th>
<th>Symptomatic Benefit</th>
<th>Overall BR</th>
<th>Symptomatic Benefit</th>
<th>Overall BR</th>
<th>Symptomatic Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>FES-8</td>
<td>47.0</td>
<td>7.1</td>
<td>47.0</td>
<td>7.1</td>
<td>47.0</td>
<td>7.1</td>
<td></td>
</tr>
<tr>
<td>TOL-4</td>
<td>44.7</td>
<td>26.9</td>
<td>44.7</td>
<td>26.9</td>
<td>44.7</td>
<td>26.9</td>
<td></td>
</tr>
<tr>
<td>FES-4</td>
<td>47.0</td>
<td>7.1</td>
<td>47.0</td>
<td>7.1</td>
<td>47.0</td>
<td>7.1</td>
<td></td>
</tr>
<tr>
<td>FES 4/8</td>
<td>47.0</td>
<td>7.1</td>
<td>47.0</td>
<td>7.1</td>
<td>47.0</td>
<td>7.1</td>
<td></td>
</tr>
<tr>
<td>PBO</td>
<td>29.0</td>
<td>26.9</td>
<td>29.0</td>
<td>26.9</td>
<td>29.0</td>
<td>26.9</td>
<td></td>
</tr>
</tbody>
</table>

### Symptomatic Benefits

- Symptomatic benefit criteria: Urgency/UII, frequency, dry mouth, constipation/headache, dizziness, retention, and tachycardia.

### Unfavourable Effects

- Unfavourable effect criteria: Urgency/UII, frequency, dry mouth, constipation/headache, dizziness, retention, and tachycardia.

## 4 Conclusions

- The full MCDA model was applied to assess the BR profiles of different OAB treatments and to compare profiles across treatments. The model permits breakdown of the overall BR profile by individual symptomatic benefit and unfavourable effect criteria for each drug, allowing identification of the criteria providing the greatest and least benefit for each drug.
- Using the MCDA model, FES flexible dosing for OAB had more favourable BR profiles than fixed-dose TOL and FES.
- The MCDA model is a useful output that can compare multiple treatment options, providing clinicians with an easy-to-interpret BR analysis to help inform clinical decision making.

## 5 References


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**Figure 3. BR Profiles of TOL 4 mg, FES 4 mg, and FES Flexible Dosing (4 or 8 mg) by Individual Symptomatic Benefit and Unfavourable Effect Criteria**

**Figure 4. Comparison of FES Flexible Dosing (4 or 8 mg) With TOL 4 mg**

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**Sensitivity analyses**

- The model was robust in sensitivity analyses, confirming that results were relatively unchanged even with significant changes in weighting or to the published evidence.

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