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# Cost-Effectiveness of Mirabegron Compared with Antimuscarinic Agents for the Treatment of Adults with Overactive Bladder in the United Kingdom

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ABSTRACT

**Background:** Mirabegron, a first-in-class selective oral $\beta_3$-adrenoceptor agonist, has similar efficacy to most antimuscarinic agents and a lower incidence of dry mouth in patients with overactive bladder (OAB). **Objectives:** To evaluate the cost-effectiveness of mirabegron 50 mg compared with oral antimuscarinic agents in adults with OAB from a UK National Health Service perspective. **Methods:** A Markov model including health states for symptom severity, treatment status, and adverse events was developed. Cycle length was 1 month, and the time horizon was 5 years. Antimuscarinic comparators were tolterodine extended release, solifenacin, fesoterodine, oxybutynin extended release and immediate release (IR), darifenacin, and trospium chloride modified release. Transition probabilities for symptom severity levels and adverse events were estimated from a mirabegron trial and a mixed treatment comparison. Estimates for other inputs were obtained from published literature or expert opinion. Quality-adjusted life-years (QALYs) and total health care costs, including costs of drug acquisition, physician visits, incontinence pad use, and botox injections, were modeled. Deterministic and probabilistic sensitivity analyses were performed. **Results:** Base-case incremental cost-effectiveness ratios ranged from £367 (vs. solifenacin 10 mg) to £15,593 (vs. oxybutynin IR 10 mg) per QALY gained. Probabilistic sensitivity analyses showed that at a willingness-to-pay threshold of £20,000/QALY gained, the probability of mirabegron 50 mg being cost-effective ranged from 70.2% versus oxybutynin IR 10 mg to 97.8% versus darifenacin 15 mg. A limitation of our analysis is the uncertainty due to the lack of direct comparisons of mirabegron with other agents; a mixed treatment comparison using rigorous methodology provided the data for the analysis, but the studies involved showed heterogeneity. **Conclusions:** Mirabegron 50 mg appears to be cost-effective compared with standard oral antimuscarinic agents for the treatment of adults with OAB from a UK National Health Service perspective.

*Keywords:* antimuscarinic drugs, cost-effectiveness analysis, mirabegron, overactive bladder.



## Introduction

Overactive bladder (OAB) is characterized by urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence [1]. The UK National Institute for Health and Clinical Excellence (NICE) recommends bladder training and lifestyle advice as first-line treatments for OAB, followed by primary pharmacotherapy with antimuscarinic agents or mirabegron (Betmiga; Astellas) [2,3]. Antimuscarinic agents are not selective because they inhibit muscarinic receptors in tissues such as salivary glands and brain, as well as those in the bladder, the therapeutic target in patients with OAB. This lack of specificity results in adverse events (AEs) such as dry mouth, blurred vision, and constipation [4], which adversely affect treatment adherence and persistence [5]; dry mouth is a common cause of treatment withdrawal [6]. In contrast, mirabegron, a first-in-class selective oral $\beta_3$-adrenoceptor agonist that enhances urine storage through stimulation of bladder $\beta_3$-adrenoceptors, has similar efficacy to antimuscarinic therapy, but improved tolerability, with an incidence of dry mouth similar to that with placebo [7–10].

We developed a Markov model to analyze the cost-effectiveness of mirabegron compared with oral antimuscarinic agents for the treatment of adults with OAB from a UK National Health Service (NHS) perspective.

## Methods

### Model Overview

We developed a Markov model to simulate the therapeutic management of OAB, including AEs of treatment, and to predict costs and

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quality-adjusted life-years (QALYs) gained after treatment with mirabegron 50 mg or antimuscarinic therapy. Data from a mixed treatment comparison (MTC) were used to estimate differences in mean changes from baseline in daily numbers of micturition and incontinence episodes and odds ratios of AEs between mirabegron and antimuscarinic agents [11]. Estimates for other probabilities, resources, and costs were obtained from the literature. Additional input regarding parameters with limited data was obtained from six clinical experts.

The cycle length of the model was 1 month, and the time horizon was 5 years; real-world data show that 65% to 86.5% of the patients discontinue therapy within 1 year [12]. The model was programmed in Microsoft Excel 2007.

## MTC

A Bayesian MTC based on a systematic literature search was used to estimate the relative efficacy and safety of mirabegron compared with placebo and the following antimuscarinic agents: tolterodine extended release (ER) 4 mg and immediate release (IR) 4 mg; darifenacin 7.5 or 15 mg; solifenacin 5 or 10 mg; fesoterodine 4 or 8 mg; oxybutynin ER 10 mg and IR 10 or 15 mg; and trospium chloride modified release 60 mg [11].

## Health States

The following elements were used to define the health states that were considered:

1. *OAB severity* based on daily numbers of micturition and incontinence episodes. These symptoms of OAB were found to have a significant influence on utility independently of each other, with moderate correlations between changes in these symptoms (unpublished data captured in 2012). The progression of each of these symptoms over time was therefore modeled separately. Each symptom had five severity levels, which were assigned a different utility decrement, and was considered independently.
2. *Treatment status for OAB*.
3. *Presence or absence of AEs*, specifically dry mouth and constipation, which had a direct effect on utilities and were associated with an increased probability of treatment switch or discontinuation.

These events are associated with antimuscarinic agents [4]; the events reported most frequently with mirabegron occur at a similar incidence as with placebo [9].

A model transition diagram is shown in Figure 1. At model entry, patients were distributed across 25 symptom severity profiles and were assigned to treatment with either mirabegron or an antimuscarinic agent. Each month, the symptom severity profile was reassessed according to changes in the frequency of micturition and incontinence. Probabilities of symptomatic changes were dependent on treatment status.

## Treatment Pathway

At model entry, patients were assigned to treatment with oral mirabegron 50 mg once daily or an antimuscarinic agent (Fig. 2). Every month, patients could switch to the next line of OAB treatment in case of treatment failure or AEs. In case of failure of the next line of therapy, a small proportion of patients received botulinum toxin (BTX); this was based on UK clinical practice as validated by a panel of experts (unpublished data captured in 2012). The model did not allow for treatment with an antimuscarinic agent after failure of BTX.

## Model Input Parameters

### Baseline symptom severity

The initial distribution of patients by symptom severity level was obtained from the phase 3 SCORPIO trial of mirabegron, based on pooled data from all treatment arms at baseline (see Appendix Table 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.05.011). SCORPIO is the name used for trial 178-CL-046, registered as NCT00689104. The official title is: A Randomized, Double-Blind, Parallel Group, Placebo and Active Controlled, Multicenter Study to Assess the Efficacy and Safety of Mirabegron in Subjects With Symptoms of Overactive Bladder.

### Transition probabilities between symptom severity levels

Transition probabilities between symptom severity levels were derived from multinomial logistic equations. We initially estimated a multinomial logistic model by regression analysis on data from the SCORPIO trial [9]. Because there were five levels of severity, the model included four coefficients capturing the effect of treatment on the probabilities of moving to different severity levels. Other covariates included in the model were sex, age, and current severity level. A calibration method was then used [13] to fit this model to mean changes in symptoms at 3 months, determined from the MTC for different products. The parameters

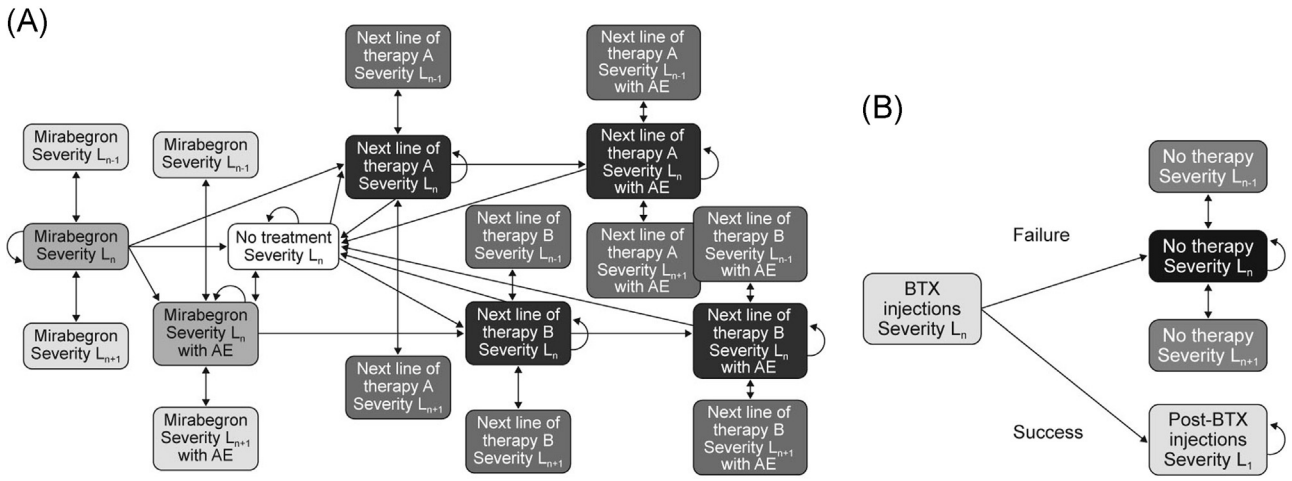


**Fig. 1 – Model transition diagram: (A) before initiation of BTX and (B) after initiation of BTX. AE, adverse event; BTX, botulinum toxin; Severity L, symptom severity level.**