ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

Drugs for the Treatment of Overactive Bladder (OAB) Syndrome

FINAL PHARMACOECONOMICS REPORT

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Conflict of Interest Statement

No study members report any affiliations or financial involvement (e.g., employment, consultancies, honoraria, stock options, expert testimony, grants or patents received or pending, or royalties) that may present a potential conflict of interest in the overactive bladder (OAB) Drug Class Review

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Note

Some details are censored in this report so as not to preclude publication. Publications (when available) and/or final unpublished reports will be available on the ODPRN website (www.odprn.ca).

Executive Briefing

- This report assessed the current evidence regarding the comparative cost-effectiveness of pharmacotherapies in the treatment of overactive bladder (OAB) syndrome and analyzed the economic impact of alternative changes to the funding status of relevant pharmacologic treatments.

- Previously published studies, including three Canadian economic evaluations, were generally of poor quality. Most studies (88%) cited financial support or affiliation with the pharmaceutical industry. The availability of well-designed independent analyses from the Canadian perspective is lacking; as such, a de novo model was developed to address the research question.

- An independent de novo economic model was developed to assess the cost effectiveness of alternative therapies for overactive bladder, as compared with each other or no therapy. A Markov model was developed which modelled the impact of treatment on the frequency of micturitions and incontinence episodes over a 12 month period.

- Solifenacin is the most cost effective therapy for the treatment of OAB. Oxybutynin immediate release (IR) may be a cost effective therapy in patients discontinuing solifenacin. Mirabegron, trospium and fesoterodine may be cost effective in patients discontinuing both solifenacin and oxybutynin IR if restricted to specific patient subgroups based on symptom levels. Darifenacin, oxybutynin extended release (ER), transdermal oxybutynin, oxybutynin gel, tolterodine ER and tolterodine IR are not cost effective based on a commonly used threshold of $50,000 per QALY gained.

- If there were no change in mirabegron prescribing from 2016 to 2018, enforcement of step therapy for anticholinergic medications would generate a reduction in overall OAB medication expenditure (-23% for patients younger than 65 years; -31% for patients 65 years and older) if this did not lead to an increase in time on all therapies. However, enforcement of step therapy for anticholinergic medications would generate an increase in overall OAB medication expenditure if there was no change in time on individual therapies.

- If mirabegron prescribing were to increase by either 10% or 20% per annum from 2016 to 2018, there would be limited effect on overall OAB medication expenditure if there were no change to current coverage. If mirabegron expenditure increased, enforcement of step therapy for anticholinergic agents with no increase in time on all therapies would still generate a reduction in overall OAB medication expenditure by the end of 2018, though the reduction will be slightly smaller.

- The reimbursement based economic evaluation found that a strategy of enforcing step therapy (i.e. using oxybutynin IR as first line therapy) would be cost effective compared to strategies involving no change to current reimbursement, adding oxybutynin ER, oxybutynin transdermal and tolterodine ER to the formulary as Limited Use and moving solifenacin and tolterodine IR to general benefit. However, given the results of the de novo economic modelling, a strategy whereby solifenacin and oxybutynin IR were considered as first line therapies with enforcement of step therapy was the most cost effective scenario.
- Analysis supports the enforcement of step therapy whereby oxybutynin IR or solifenacin are considered first line therapy. Analysis suggests that suitable second line therapies may be mirabegron, fesoterodine and trospium. Darifenacin, oxybutynin ER, transdermal oxybutynin, oxybutynin gel, tolterodine ER and tolterodine IR are not cost effective.

List of abbreviations	
ACh	anticholinergic
BID	two times per day
BTX	botulinum toxin A injection
CAD	Canadian dollar
CCA	cost-consequence analysis
CEA	cost-effectiveness analysis
CMA	cost-minimization analysis
CR	controlled-release
CUA	cost-utility analysis
DAR	Darifenacin
EQ-5D	European Quality of Life – 5 Dimensions
ER	extended-release
EUR	Euro
FES	Fesoterodine
GBP	British pound
HCP	health care payer
ICER	Incremental cost-effectiveness ratio
IR	immediate-release
KT	Kylie Tingley
ML	Mirhad Lončar
MYR	Mirabegron
OAB	overactive bladder
OXY	Oxybutynin
QALY	quality-adjusted life year
RCT	randomized controlled trial
SOL	Solifenacin
TID	three times per day
TOL	Tolterodine
TRO	Trospium
UK	United Kingdom
USA	United States
USD	US dollar
XL	extended-release

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RQ4. Based on a de novo economic model, what is the cost-effectiveness of alternative policies for reimbursing pharmacologic treatments for OAB syndrome?

Systematic Review of Published Economic Evaluations

In brief, this review highlights the current published evidence on the comparative cost-effectiveness of pharmacologic treatments in the management of adults with overactive bladder (OAB) syndrome. Few independent analyses were identified in the published literature which examined the cost-effectiveness of currently available OAB medications, including anticholinergic urologic agents (darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium), beta-3 adrenergic agonist mirabegron, and neuromuscular blocker botulinum toxin A. The majority of included economic evaluations expressly cited financial support from the pharmaceutical industry or had authors who were affiliated with industry, and study findings consistently favoured the sponsor's product. The paucity of well conducted independent analyses from the Canadian perspective precluded any inferences regarding the cost-effectiveness of drug therapies for OAB treatment in Canada.

Of the 26 published economic evaluations identified in this review, most studies (cost-utility analyses, cost-effectiveness studies, cost-effectiveness/cost-utility studies, cost-minimization analyses, as well as a cost-consequence study and a cost-consequence/cost-effectiveness analysis) were conducted across a range of European settings; three Canadian economic analyses were also identified. Included studies varied in their approach to modeling costs and benefits associated with chosen treatment comparators; yet, given that most studies were industry-sponsored or affiliated with industry, results tended to favour the sponsor's product. In addition to the proportion of industry-funded studies, a number of limitations were common across all evaluations, including issues related to the derivation of utility values, as well as modeling of treatment discontinuation and adverse events. In addition, the inclusion of costs related to incontinence pad use in studies' base case analyses limits generalizability to the Ontario context, as pads are not covered by the Ministry of Health and Long Term Care in Ontario. On the whole, the applicability of study findings to the current decision-making context was generally poor as the research questions did not align with question being posed in this review.

When focusing on Canadian studies specifically, which are likely to be more closely aligned with the current decision-making context and use Canadian specific parameters, there were a total of three economic evaluations which examined the cost-effectiveness of anticholinergic medications in the treatment adults with OAB symptoms. Two of these studies were published more than 10 years ago and their findings do not accurately reflect current clinical evidence or cost data. These three evaluations were also limited by their narrow research questions, receipt of industry funding, as well as issues related to the extrapolation of short-term efficacy data from single clinical trials, the handling of treatment discontinuation rates and adverse events, and the inclusion of costs of incontinence pads. Therefore, although these economic

evaluations may reflect the context of the Canadian health care decision maker, drawbacks related to their analytic approach and choice of comparators weaken the applicability of the results.

Two independent analyses were also included in this review. While the applicability of the study findings was strengthened by their consideration for a broad range of treatment comparators and the absence of industry sponsorship or affiliation, a number of limitations similar to those identified within industry-funded research were identified. Accordingly, these analyses are not sufficiently useful in aiding decision making within the Canadian context.

Given the shortcomings within the published literature, limiting the applicability and generalizability of the available cost-effectiveness evidence, a de-novo economic model which incorporates more recent evidence form the Canadian context is required to assess the comparative cost-effectiveness of this class of drug therapies.

For a detailed report of the review of economic literature regarding this drug class, refer to Appendix A – Systematic Review of Economic Evidence.

De novo Economic Evaluation

An independent de novo economic model was developed to assess the cost effectiveness of OAB therapies in the Canadian context. The costs and quality adjusted life years (QALYs) of oxybutynin IR, oxybutynin ER, oxybutynin gel, oxybutynin transdermal, tolterodine IR, tolterodine ER, solifenacin, fesoterodine, trospium, darifenacin, mirabegron and no drug treatment (no therapy) were compared, in the management of overactive bladder were estimated. A Markov model was developed to compare the therapies over a twelve month period with monthly cycles.

A cohort of patients initiates first line OAB therapy upon entering the model. With each cycle, patients either remain on therapy or discontinue first line OAB therapy. In those who discontinue first line OAB therapy, a portion go on to receive second line OAB therapy, a portion experience resolution of their symptoms and a portion discontinue all OAB therapy, but continue to experience OAB symptoms. With each cycle, patients who receive second line OAB therapy may either continue with treatment or discontinue due to either resolution of symptoms or due to other reasons. If they discontinue due to other reasons, their symptoms are assumed to be equivalent to those receiving no therapy.

Disease states within the model were defined based on symptoms, specifically the number of micturitions per 24 hours and the number of incontinence episodes per 24 hours. The companion network meta-analysis provided estimates of the improvement in symptoms with each treatment at three months as compared with placebo. Long term Ontario real world prescription data were used to estimate persistence with therapy and switches to alternative OAB treatment. Detailed deterministic and probabilistic sensitivity analyses were conducted.

Solifenacin is the most cost effective therapy for the treatment of OAB with an ICER of $19,050 per QALY versus no therapy. Solifenacin dominates all other treatments except oxybutynin IR, which is subject to extended dominance through solifenacin and no therapy. In comparing other treatments with no therapy, oxybutynin IR has an ICER of $27,442 per QALY and the ICERs for mirabegron ($51,197 per QALY), trospium ($53,171 per QALY) and fesoterodine ($56,168 per QALY) compared with no therapy are just higher than the frequently sited willingness to pay threshold of $50,000 per QALY.

The results of this analysis show that solifenacin is the most cost effective therapy for the treatment of OAB. The generic price of solifenacin is considerably lower than other branded products, offering potential savings in the treatment of OAB. Given the high discontinuation

rates with all OAB therapies, many patients will go on to alternative treatments after solifenacin. Mirabegron, trospium and fesoterodine may be cost effective in patients discontinuing both solifenacin and oxybutynin IR if restricted to specific patient subgroups based on symptom levels. Darifenacin, oxybutynin ER, transdermal oxybutynin, oxybutynin gel, tolterodine ER and tolterodine IR are not cost effective based on a commonly used threshold of $50,000 per QALY gained.

A detailed description of the methods and results from the economic model is provided in Appendix B – De novo Economic Evaluation.

Budget Impact Analysis

Among persons aged less than 65 years, total spending on OAB anticholinergic agents has risen from about $1.0 million in 2000 to $6.1 million in 2014. During the same time period, total expenditure on anticholinergic medications among those aged 65 years and older has increased from about $4.5 million to over $31.3 million. To date, anticholinergic urologic agents have accounted for the majority of OPDP expenditure for OAB medications among all patient groups. In May 2015, beta-3 adrenergic agonist mirabegron was listed as a limited use benefit on the ODB formulary.

Without any changes to current reimbursement for OAB medications and the expected availability of generic solifenacin by the end of 2015, OAB medication expenditure is expected to decrease to $6.0 million for patients aged less than 65 years and to $30.4 million for patients aged 65 years and older by the end of 2018.

If there were no change in mirabegron prescribing from 2016 to 2018, enforcement of step therapy for anticholinergic medications would generate a reduction in overall OAB medication expenditure (-23% for patients younger than 65 years; -31% for patients 65 years and older) if this did not lead to an increase in time on all therapies (strategy 2a). However, enforcement of step therapy for anticholinergic medications would generate an increase in overall OAB medication expenditure if there was no change in time on individual therapies (strategy 3a).

A General Benefit listing for oxybutynin and solifenacin with all other agents listed as Limited Use (strategy 5a) or a General Benefit listing for solifenacin with all other agents on Limited Use access (strategy 5b) would not lead to a decrease in expenditure for OAB medications by the end of 2018.

If mirabegron prescribing were to increase by either 10% or 20% per annum over the next three years, there would be limited effect on overall OAB medication expenditure if there were no change to current coverage. If mirabegron expenditure increased, enforcement of step therapy for anticholinergic agents with no increase in time on all therapies (strategy 2d) would still generate a reduction in overall OAB medication expenditure by the end of 2018, though the reduction will be slightly smaller.

Refer to Appendix C – Budget Impact Analysis for a detailed report of the reimbursement-based economic assessment.

Reimbursement-based Economic Evaluation

Analysis estimated the cost effectiveness of the alternative strategies considered within the budget impact analysis. The following strategies were considered:

- status quo,
- status quo plus listing oxybutynin transdermal, oxybutynin ER and oxybutynin gel as limited use products,

- enforcement of step therapy (require first line use of oxybutynin IR),
- enforcement of step therapy with listing oxybutynin transdermal, oxybutynin ER and oxybutynin gel as Limited Use products,
- moving solifenacin and tolterodine IR to General Benefit,
- moving solifenacin and tolterodine IR to General Benefit with listing oxybutynin transdermal, oxybutynin ER and oxybutynin gel as Limited Use products

Analysis was conducted assuming no increase in mirabegron prescribing and no change in time on individual therapies with step therapy. Sensitivity analysis examined the impact of assuming a 10% annual increase in mirabegron prescribing and that enforcement of step therapy would lead to no increase in total time on all therapies.

The costs and QALYs associated with each strategy were estimated by weighting the costs and QALYs associated with each individual therapy by their percentage usage as estimated through the budget impact analysis.

Analysis found that a strategy of enforcing step therapy (i.e. using oxybutynin IR as first line therapy) would be cost effective compared to the original strategies considered. The incremental cost per QALY gained for this strategy versus status quo was $15,062. This finding was robust within sensitivity analysis.

The results of the de novo economic modelling found solifenacin to be cost effective compared to all other therapies. Thus, two additional strategies were considered whereby solifenacin was moved to general benefit and solifenacin was considered a first line therapy as per oxybutynin IR with enforcement of step therapy. The strategy whereby solifenacin and oxybutynin IR were considered as first line therapies with enforcement of step therapy was optimal, dominating the status quo.

Appendices

Appendix A – Systematic Review of Economic Evidence

Research Question

What is the current evidence for the comparative cost-effectiveness of pharmacologic treatments for overactive bladder (OAB) syndrome?

Review of Published Literature

Search Strategy and Search Findings

Search Strategy

A search of the medical literature was conducted in Ovid MEDLINE (indexed, in-process and other non-indexed citations) from 1946 to present (2015 August 19) as well as EMBASE Classic & EMBASE 1974 to present (2015 August 19) in order to capture all relevant literature. Key words relating to OAB pharmacologic treatment approved for use in Canada (darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, trospium, mirabegron, botulinum toxin A) were coupled with a standardized search strategy for identifying economic analyses adopted by the National Health Service Economic Evaluation Database (NHS EED). The complete search strategy can be found in Appendix A1: Search Strategy.

Additional citations were retrieved for screening from the Tufts CEA Registry and NHS EED databases. Grey literature was identified through the Canadian Agency for Drugs and Technologies in Health (CADTH) and the National Institute for Health and Care Excellence (NICE) websites. Finally, reference lists of included studies were hand searched for additional relevant records.

Search Findings

A total of 449 citations relating to the cost-effectiveness of treatments for OAB were identified from the initial searches, 309 of which were found through searches of electronic databases and an additional 105 records identified from grey literature sources. Following the removal of duplicate records, 410 unique citations were retrieved for screening.

Two reviewers (ML and KT) independently reviewed the titles and abstracts of studies identified by the search strategy in order to identify potential articles for critical appraisal. Namely, of the 410 unique records screened, 48 citations were selected for full-text review. Thus, a total of 362 records were excluded in the first phase of screening, and an additional 23 records were excluded following assessment of full-text articles. Any disagreements during this two-stage screening process were resolved through consensus. Exhibit 1 in Appendix A2 presents the search results, including reasons for exclusion of full-text publications.

Among the 48 articles that were retrieved for full-text review, a total of 25 studies addressed the objective of the review and were selected for inclusion. One additional study was identified through hand-searching references of selected studies and was included. A list of excluded studies along with reasons for exclusion is presented in Exhibit 2 of Appendix A3.

Included Studies

A list of included studies is presented in Exhibit 3 of Appendix A4.

Summary and Critical Appraisal of Included Studies

Included Studies

A total of 26 published economic evaluations which examined the comparative cost-effectiveness of pharmacologic treatments for OAB syndrome were included in this review. Of these studies, nine (35%) were conducted in the United Kingdom, [1-9] six (23%) were conducted in the United States,[10-15] three (12%) in Canada,[16-18] two (8%) in Sweden,[19,20] and one (4%) each in Germany,[21] Italy,[22] and Spain.[23] There were an additional three (12%) studies which were conducted across multiple European settings.[24-26] Most economic evaluations (88%) received direct sponsorship from the pharmaceutical industry,[1-11,13,14,16-19,21-26] with Astellas Pharma as the most common sponsor.[1,2,5,7-9,11,17,21,22,26] In addition, there were two independently-funded studies[12,20]; while one economic evaluation did not disclose any funding sources, the authors of the study were affiliated with industry.[15] A brief overview of the characteristics these 26 economic analyses in presented in Exhibit 4 of Appendix A5.

Twelve (46%) studies included in this review were cost-utility analyses,[1,2,4,5,8,9,15,17,20,21,23,24] while five (19%) studies were cost-effectiveness analyses [6,11,12,16,25]; five studies (19%) were both cost-effectiveness and cost-utility analyses.[3,18,19,22,26] Moreover, there were two (8%) cost-minimization analyses,[13,14] one (4%) cost-consequence analysis,[7] and one economic evaluation (4%) was both a cost-consequence and cost-effectiveness analysis.[10] Of the 26 economic evaluations, 15 (58%) used a Markov state transition model for estimating costs and outcomes,[1,3-5,7-9,15-22] while the remaining 11 (42%) used a decision tree to compare the cost-effectiveness of different OAB therapies.[2,6,10-14,23-26] The time horizon considered across included studies spanned the period from 3 months[11-13] to 5 years [1,9]; however most economic evaluations (69%) modeled disease progression over the course of one year.[2-8,14,16-24,26] Furthermore, 20 (77%) studies adopted a health care payer or third party payer perspective,[1-12,14-17,19-21,24] while four (15%) economic analyses were conducted from the societal perspective [13,18,23,25]; there were two (8%) studies which considered both the health care payer and societal perspective.[22,26]

Assessment of the comparative cost-effectiveness of OAB treatments across included studies mostly comprised direct comparisons of two or more active treatments. These included 16 (62%) studies which compared anticholinergic urologic agents against each other,[2,3,5,6,8,10-14,16,17,21,23-25] two (8%) studies comparing beta-3 adrenergic agonist mirabegron against anticholinergic medications,[1,9] and one study examined neuromuscular blocker botulinum toxin A in comparison with long-acting anticholinergic agents.[15] In addition, there were five (19%) studies which compared the cost-effectiveness of anticholinergic medications against placebo or no treatment,[4,19,20,26] and two (8%) studies examined the cost-effectiveness of different treatment sequences.[7,18]

The target populations which were considered across the selected economic evaluations typically consisted of adult patients with overactive bladder symptoms, including any combination of urinary frequency, urgency, or urge incontinence. While many studies did not report a detailed symptomatic profile of the patient group being considered,[1,2,5,6,8-14,16,19-23,26] there were three studies which specified that patients in the model were aged 18 years or older and presented with a combination of eight or more micturitions per day or one or more daily episodes of urge urinary incontinence and/or two or more urgency episodes per day.[4,17,24] Moreover, two studies considered patients with urge or mixed urinary incontinence,[3,25] and one study specifically examined female patients with refractory idiopathic urge incontinence.[15] Second-line treatment with an OAB medication was the focus of two included studies, including one economic analysis which modeled patients with OAB symptoms who were aged 40 years or older and currently receiving antimuscarinic treatment,[7] and one study which examined patients with urge incontinence who discontinued

initial treatment with an anticholinergic medication.[18]

Study outcomes were generally quantified as incremental costs per quality-adjusted life years (QALYs) gained; however, some studies measured cost-effectiveness in terms of the expected cost per treatment success (defined as zero incontinence episodes per week) and the expected cost per continent days, while other studies used similar variants such as the cost per incontinent episode avoided or the cost per additional patient achieving continence. Furthermore, of the 17 economic evaluations which measured patients' health-related quality of life, 11 studies based their utility estimates on a Swedish willingness to pay study, as derived by Kobelt et al., published in 1997[2-5,8,17-19,21,22,26]; this study assumed a linear relationship between incontinence episodes and micturitions and quality of life (as measured using the EQ-5D), and used this relationship to convert clinical symptoms to utility gains. Utility estimates in other studies included in this review were derived from a variety of sources, including the Overactive Bladder Questionnaire (OAB-q),[24] the King's Health Questionnaire (KHQ),[20,23] quality of life data collected within clinical trials using the EQ-5D instrument,[1,9] as well as the published literature.[15]

A detailed synthesis of the interventions and results of the included economic evaluations is presented in Exhibit 5 of Appendix A5.

Considerations and Limitations Relating to the Published Literature

A number of common limitations were identified across the studies included in this review, which may reduce the usefulness of the published evidence in addressing the research question for this review. A brief summary of these issues is presented below.

Canadian Content

There were three published economic evaluations which examined the comparative cost-effectiveness of pharmacologic treatments for OAB syndrome from a Canadian perspective.[16-18] Two of these studies were published more than ten years ago, which do not reflect the current clinical evidence base or cost data. In addition, none of the studies were free from industry funding or affiliation, limiting their use in aiding decision-making.

Sponsorship and Industry Affiliated Studies

Among the 26 economic evaluations included in this review, 23 studies (88%) received direct financial support from pharmaceutical manufacturers,[1-11,13,14,16-19,21-26] and the authors of one study were affiliated with industry.[15] These studies may be susceptible to biases and limitations that have been found in manufacturer-sponsored evaluations.[27]

Utility Value Derivation

Among studies which elicited utility values for inclusion in their economic analysis, these values were in many cases derived from a correlation of clinical symptoms (micturitions or voids and leakages) with a EuroQol-5 dimensional value measured at a single time point, based on a small willingness to pay study conducted in 1997, rather than from direct measurement within clinical trials. The derivation of utility values based on an assumed linear relationship between overactive bladder symptoms and quality of life is of questionable validity. Moreover, there is a lack of evidence to support the relation between changes in clinical symptoms and improvements in utility or quality of life, which undermines this approach to measuring the efficacy of OAB treatments. Finally, in many instances, the method of incorporating utilities did not include the adverse effects of medications on patient's quality of life.

Discontinuation of Therapy

The approach to modeling treatment discontinuations was noticeably different across the included studies and may have influenced the observed variation in study outcomes. In particular many studies used trial-based discontinuation rates rather than the preferred approach of estimating real world discontinuation rates

Costs of Incontinence Pads

Cost estimates relating to the use of incontinence pads and appliances were incorporated in the base-case analysis of many economic evaluations. However, incontinence pads are generally not funded by the Canadian public health care payer and inclusion of such costs in a primary analysis may limit the applicability of the results for the Canadian health care decision maker.

Adverse Events

Consideration for treatment-related adverse events was reported across 38% of included studies in this review.[1,6,9,15,17,20,23-26] Among these evaluations, patients who experienced adverse events were generally assumed to discontinue therapy. While there were two studies which applied a quality of life decrement or disutility for patients who experienced adverse events and stayed on treatment,[9,20] this approach to handing adverse events was generally not applied across other studies; given the small gains in utility that are typically associated with OAB medications, this may have a significant impact on cost-effectiveness estimates.

Canadian Studies

There were three published economic evaluations which examined the comparative cost-effectiveness of pharmacologic treatments for OAB syndrome from a Canadian perspective. A summary of each of these studies, along with an assessment of their limitations, is provided below.

Getsios et al. (2004) Clin Ther

Getsios et al. compared the cost-effectiveness of oxybutynin XL (10 mg/day) and tolterodine IR (2 mg BID) in community-dwelling adults with OAB syndrome. A Markov-based model was run over a 1 year time frame with biweekly cycles for the first four weeks, followed by monthly cycles for the remainder of the time horizon. Progression of disease was modeled based on data obtained from a 12-week RCT (OBJECT study), extrapolated to 1 year, which measured disease severity along five distinct severity states based on patients' total urinary incontinence (TUI) episodes per week. Rates of treatment persistence were also derived from this single head-to-head trial. The analysis was conducted from the perspective of the Canadian health care payer, incorporating costs of OAB medications, physician visits, incontinence pads, and laundry costs, with all estimates presented in 2002 Canadian dollars.

Results of the base-case analysis suggested that oxybutynin XL dominated tolterodine IR, with 16.5 additional incontinence-free days and annual cost savings of $32 among patients receiving oxybutynin XL, as compared with users of tolterodine IR. The robustness of the model was evaluated through deterministic sensitivity analysis; while results were robust to changes in assumptions regarding discontinuation of therapy, findings were sensitive to the relative cost of the two medications.

On the whole, this study appeared well designed and adopted the perspective of Canadian health payer. Certain factors may nonetheless limit its use in aiding decision making within this context. In particular, the restricted choice of comparators makes it difficult to assess the

relative cost-effectiveness of other, newer OAB medications. Further, the lack of long-term data supporting sustained treatment effects with OAB medications brings into question the validity of extrapolating short-term clinical trial data. Another drawback of this study stems from the derivation of treatment persistence rates from clinical trials as this may overestimate persistence with therapy, as compared with rates derived from real world databases. The inclusion of incontinence pads and appliances is a cost that is generally not borne by the Canadian public health care payer and further limits the applicability of the results. Moreover, the interpretability of this study is limited due to the difficulty of valuing an incontinence-free day. Similar to most studies in this area, this economic evaluation received pharmaceutical industry sponsorship. Given the date of the study (2004), the current clinical evidence base and cost data are unlikely to be reflected.

Herschorn et al. (2010)

Herschorn et al. conducted a cost-utility analysis comparing OAB urologic agents solifenacin (5 mg/day) and oxybutynin IR (5 mg TID) in adult patients with one or more daily urgency episodes (with or without urgency urinary incontinence) and eight or more micturitions per day for 3 or more months. The evaluation was conducted using a five-state Markov model based on OAB severity and run over a 1 year time horizon with monthly cycles. Data on treatment efficacy (i.e. frequency of micturitions and leakages) were derived from a single 8-week RCT (VECTOR study) whose primary aim was to assess the comparative incidence of dry mouth with the two medications; discontinuation rates were derived from a provincial claims database. Cost estimates relating to OAB medications were included in the base-case analysis, while the cost of incontinence pads was considered as part of a sensitivity analysis. Utility estimates were elicited from a Swedish willingness to pay study, as derived by Kobelt et al., with study outcomes reported as incremental costs per QALY gained (ICER). The analysis was conducted from the perspective of the Canadian health care payer, with all costs presented in 2009 Canadian dollars.

Base-case results showed that treatment with solifenacin is associated an ICER of $14,092 per QALY gained in comparison with oxybutynin IR. Furthermore, solifenacin was found to be cost-effective in approximately 90% of Monte Carlo simulations at a willingness-to-pay threshold of $50,000 per QALY. When the costs of incontinence pads were included in the model, treatment with solifenacin was dominant over oxybutynin IR. Study findings were most sensitive to discontinuation rates and the inclusion of costs of incontinence pads, as well as assumptions regarding treatment and utility for those who discontinue therapy.

Overall, while this study adopted the Canadian perspective, its applicability within the current decision making setting remains limited as a result of a number of weaknesses which preclude a clear interpretation of results. First, the narrow choice of comparators provides an incomplete picture of the relative cost-effectiveness of other, newer OAB medications. Second, the economic model assumes that the 8-week efficacy results would be maintained throughout the study's one-year time horizon, as long as the patient did not discontinue therapy; however, this assumption is problematic given the lack of clinical data supporting the sustained effects of long-term treatment with an OAB agent. Third, concerns regarding the derivation of utilities based on a linear relationship between frequency of symptoms and utilities, as previously discussed, also applies to this study. Furthermore, assumptions regarding the costs and utilities assigned to patients who discontinued therapy within this model appear inappropriate and biased in favour of solifenacin. Namely, discontinuing patients in the base-case analysis were assumed to receive second-line treatment with tolterodine ER, but achieved a utility gain lower than the baseline value of the modeled cohort (i.e., drop-out utility value calculated as the average of utilities of the health states within the model); however, in the sensitivity analysis in which patients did not incur the cost of tolterodine, their utility gains were still lower than their baseline values. When utility gains for discontinuing patients were assumed to be slightly greater than the baseline average for the

modeled cohort, an ICER of $318,111 per QALY was generated for solifenacin in comparison with oxybutynin IR; this ultimately shows that the utility value associated with discontinuation of therapy appears to have a considerable impact on study results and conclusions. Finally, this study received financial support from the pharmaceutical industry (Astellas Pharma Canada, Inc.), which significantly reduces its usefulness in aiding decision making.

O'Brien et al. (2001)

O'Brien et al. examined the cost-effectiveness of second line treatment with tolterodine (2 mg BID) in comparison with no pharmacologic treatment in adult patients with urge incontinence that discontinued initial therapy with generic oxybutynin IR. These two treatment strategies were modeled using a four-state Markov model over a 1-year time horizon with 4-week cycles. Treatment efficacy inputs were obtained from the pooled results of three head-to-head 12-week RCTs which compared tolterodine (2 mg BID) and oxybutynin (5 mg TID), and rates of treatment discontinuation were derived from two sources: trial-based rates of discontinuation of therapy and the Quebec provincial drug claims database. The analysis was conducted from the perspective of the Canadian health care payer and the societal perspective, incorporating costs of OAB medications physician visits, and incontinence pads. The final outcome of the analysis was expressed in terms of both the incremental cost per QALY gained and the cost per number of months in "normal" health state (i.e. no leakages); utility values for incontinence health states were derived from the study by Kobelt et al.

Base-case findings revealed that oxybutynin followed by tolterodine generated an ICER of $9982 per QALY gained as compared with oxybutynin followed by no treatment. Moreover, second-line use of tolterodine after discontinuation of oxybutynin results in an average of 1.15 months in the normal health state in comparison with 0.5 months in the normal state spent by patients who discontinued oxybutynin and received no further therapy; therefore, second-line use of tolterodine was associated with an increase of 0.65 months in the normal health state. The model's robustness was assessed by way of a deterministic sensitivity analysis; the authors found that results were insensitive to changes in the baseline disease state distribution of the modeled cohort, the oxybutynin dose distribution, as well as changes in costs and utilities. Rates of treatment discontinuation were not tested within sensitivity analyses.

Overall, while the applicability of this study is strengthened by the fact that it was conducted from the Canadian perspective, several factors limit its usefulness in aiding decision making within this context. First, the efficacy data from the clinical trials was extrapolated to the model's one year time frame assuming that the 12-week efficacy persisted throughout this time period; however, this assumption is unsupported by longer term data regarding the maintenance of treatment effect. Second, the authors assumed that all patients who discontinued therapy with oxybutynin IR did so either as a result of intolerance or lack of efficacy, and no one discontinued due to a resolution of symptoms; treatment discontinuation due to symptom resolution would necessarily affect the proportion of persons eligible for second-line therapy with tolterodine IR. Moreover, because rates of treatment discontinuation were derived from a combination of clinical trial data and a real world drug claims database, trial-based discontinuation rates were inflated by a factor of 2.9 (as informed by a higher rate of discontinuation of oxybutynin IR in the 'real world'), which resulted in the assumption of a proportional or relative difference in discontinuation between the two treatments rather than an absolute difference. Although this assumption appears inappropriate and potentially biased in favour of tolterodine IR, its true impact on the results of this analysis is unknown in the absence overt testing within sensitivity analyses. Another limitation of this analysis relates to the assumption that discontinuing patients who received no further pharmacological treatment achieved no improvement in symptoms or quality of life, as compared with experiencing a placebo response. Further, adverse events were not explicitly incorporated within the model aside from accounting for them within the estimated discontinuation rates, and no disutility

was applied to patients who experienced adverse events and remained on therapy. The applicability of this analysis is also limited by the inclusion of costs of incontinence pads which are generally not relevant to the Canadian health care payer, and the drawback associated with using the Kobelt et al. approach to covert OAB symptoms to utility values also applies to this study. Finally, the age of the study, its narrow range of comparators, and receipt of industry funding significantly restricts its usefulness in informing decisions concerning the funding status of currently available OAB medications.

Non-Canadian Studies

Independent studies

Ko et al. (2006)

Ko et al. examined the comparative cost-effectiveness of eight anticholinergic medications for the management of adult patients with overactive bladder symptoms. The treatment comparators comprised oxybutynin IR (5 mg TID), oxybutynin ER (10 mg/day), transdermal oxybutynin patch (3.9 mg/3-4 days), tolterodine IR (2 mg BID), tolterodine ER (4mg/day), darifenacin (15 mg/day), solifenacin (5 mg/day) and trospium (20 mg BID). Cost-effectiveness was modeled using a decision tree run over a 3-month time horizon, and the perspective adopted in the analysis was that of the US health care payer. Treatment efficacy data and discontinuation rates of the anticholinergic agents used in the model were obtained from the published literature (selected RCTs), with treatment success defined as complete continence (i.e. no incontinence episodes or 7 consecutive dry days). The costs included within the model were for OAB medications and comorbidities including urinary tract infections, skin infections, depression, and fractures, with the rate of comorbidities being dependent on the degree of urinary incontinence control; all costs were presented in 2005 US dollars. The final outcome of the analysis was expressed in terms of the average cost per patient with continued or successful treatment, defined as achievement of complete continence.

Results of the base-case analysis revealed that solifenacin dominated all other antimuscarinic agents as it was associated with both lower costs and higher efficacy than the modeled comparators; however, deterministic sensitivity analysis revealed that results were sensitive to changes in treatment success rates, but remained robust to changes in discontinuation rates and costs of medications and OAB-induced comorbidities.

Although the analytic approach adopted in this economic evaluation was comprehensive, as demonstrated by the inclusion of many pharmacologic treatments for OAB syndrome, study findings warrant careful interpretation in light of several limitations. First, the interpretability of study findings is unclear given the difficulty in interpreting the clinical meaningfulness of the effectiveness measure. This study is also limited by the fact that it modeled patients over a 3 month period and did not appear to test this duration within sensitivity analyses; this is problematic since it is unlikely that patients would be treated for such a short period of time. Of particular concern is the inclusion of costs relating to comorbidities associated with overactive bladder given the lack of clinical evidence which supports a reduction in these comorbidities among patients who achieve complete continence as a result of pharmacologic treatment. There is also a lack of transparency regarding the adjustment of comorbidity rates for low, medium, and high risk patients, and there is no evidence that these assumptions have been tested within sensitivity analyses, which may impact the results of the study. Additionally, the cited reference relating to the rate of OAB-induced fractures shows a link between incontinence and falls, rather than incontinence and fractures; therefore, the authors appear the erroneously assume that these are the same, and incorporate a rate for falls rather than fractures. Furthermore, the rates of treatment discontinuation used within this evaluation were derived from clinical trials, which have been shown to underestimate true discontinuation rates observed in clinical practice. Discontinuing patients were also assumed

to stop treatment exclusively due to adverse events, while discontinuation of therapy due to lack of efficacy or resolution of symptoms was not accounted for. Finally, the applicability of this study is limited for the Canadian context given that the analysis adopted a US perspective, which has a significantly different healthcare system than Canada.

Nilsson et al. (2011)

Nilsson et al. conducted a cost-utility analysis comparing newer anticholinergic agents (solifenacin, tolterodine, fesoterodine, darifenacin, and oxybutynin patch) with oxybutynin IR (5 mg TID), no treatment and placebo treatment in adult patients with urgency urinary incontinence. In the no treatment arm, patients were assumed to experience no improvement in symptoms or quality of life, whereas in the placebo treatment arm, the placebo response from clinical trials was used to estimate any improvement in quality of life. The analysis was conducted using a three-state Markov model based on treatment administration and run over a 1-year time horizon with 2-week cycles. Treatment efficacy inputs and rates of discontinuation of therapy were sourced from patients within the Swedish Prescribed Drug Registry who previously received OAB medications, with the assumption that treatment was effective in all patients who refilled their prescription at least once within 120 days of the original prescription. The analysis was conducted from the perspective of the Swedish health care payer, incorporating costs of OAB medications, physician visits, incontinence pads, and dementia investigation costs; all costs were presented in 2010 Euro (€) values. Utility values were obtained from two fesoterodine studies which used the King's Health Questionnaire (KHQ) to estimate improvements in quality of life, and the final outcomes of the analysis were reported as incremental costs per QALY gained (ICER).

Base-case results showed that treatment with newer anticholinergic medications generated and ICER of €37,119 (1.00 € = 1.51 CAD; 2010) per QALY gained when compared with oxybutynin IR. Conversely, newer anticholinergic agents were associated with an ICER of €21,045 per QALY gained and an ICER of €65,435 per QALY gained in comparison with no pharmacologic treatment and placebo treatment, respectively. Deterministic sensitivity analysis revealed that results were sensitive to changes in the cost of incontinence pads, very serious adverse events, and the probability of non-responders receiving alternative therapy.

Overall, while the applicability of this study is strengthened by the absence of industry sponsorship, the inclusion of quality of life estimates which were directly measured within fesoterodine clinical trials using a validated instrument, and the fact that treatment discontinuation rates were derived from a real world database, a number of limitations were identified. Namely, efficacy inputs were based on fesoterodine studies which may have an efficacy benefit over newer anticholinergic medications; however, fesoterodine may also have a greater risk of adverse events than newer anticholinergic agents, which was not accounted for in the model. Further, the author's assumption that those patients who refilled their prescription within 120 days experienced treatment efficacy and those who didn't were non-responders may not be justified; there may be other reasons why patients do not renew their prescription (e.g., resolution of symptoms), and similarly, a prescription may be renewed even if response to treatment has not been experienced. Additionally, long term compliance with the modeled OAB medications may have been overestimated by using 12-week treatment discontinuation rates rather than 1-year discontinuation rates from the aforementioned claims database. The validity of grouping all newer anticholinergics together and assuming a comparable safety and efficacy profile is highly questionable and poorly justified by the study authors. This analysis may also be limited by in its disregard to incorporate a disutility estimate for patients who experience an adverse event but remain on therapy. Finally, the perspective of the Swedish health care payer is of limited applicability to the Canadian health care decision maker given that treatment patterns may differ between the countries and the fact that costs associated with incontinence pad use are generally not borne by the Canadian

health care payer.

Industry-sponsored and industry-affiliated studies

There were 21 economic evaluations conducted outside of Canada which received financial support from the pharmaceutical industry or whose authors were affiliated with industry. Of these studies, 10 (48%) were cost-utility analyses,[1,2,4,5,8,9,15,21,23,24] three (14%) were cost-effectiveness analyses,[6,25,28] and four (19%) were both cost-effectiveness and cost-utility analyses.[3,19,22,26] There were also two (10%) published cost-minimization analyses,[13,14] one (5%) cost-consequence analysis,[7] and one study was a cost-consequence and cost-effectiveness analysis.[10] Markov health state transition models were used in about one half (52%) of these evaluations,[1,3-5,7-9,15,19,21,22] while the remaining 11 (48%) studies used a decision tree to assess cost-effectiveness.[2,6,10,11,13,14,23-26] Furthermore, the study time horizons spanned the period from 3 months[11,13] to 5 years,[1,9] with 67% of analyses adopting a 1-year time frame.[2-8,14,19,21-24,26] Seventy-six percent of the industry-sponsored or industry-affiliated studies were conducted from the perspective of the health care payer or third party payer[1-11,14,15,19,21,24]; conversely, three studies adopted the societal perspective,[13,23,25] and two other studies considered both the health care payer and societal perspectives within their analysis.[22,26]

In the eleven studies sponsored by Astellas Pharma and its subsidiary Yamanouchi Europe, results were generally positive and favourable toward solifenacin (9 studies) or mirabegron (3 studies).[1,2,4,5,7-9,11,21,22,26] In the five studies which received financial support from Pfizer or its subsidiary Pharmacia & Upjohn, results consistently demonstrated that tolterodine or fesoterodine was either cost-saving or dominant over other selected comparators.[13,14,19,23,24] Moreover, economic analyses which received sponsorship from Janssen Pharmaceutica, Sanofi-Snthélabo, or Alza Corporation were all supportive of extended-release oxybutynin as the most cost-effective treatment option relative to other comparators.[3,6,10,25] Finally, in a cost-utility analysis whose authors were affiliated with Allegan, botulinum toxin A injections were found to be more cost-effective than treatment with long-acting anticholinergic medications in the treatment of refractory idiopathic urge incontinence among women.[15] In brief, the sponsor's product was favoured in all cases. This finding is not surprising and mirrors previous work relating to industry-funded pharmacoeconomic studies.[27]

Overall Conclusions

On the whole, the available evidence relating to the comparative cost-effectiveness of pharmacologic treatments for the management of adults with overactive bladder symptoms is generally of poor quality, with the majority of studies disclosing financial support or affiliation with the pharmaceutical industry. Although three Canadian economic evaluations were identified, all studies were sponsored by a pharmaceutical manufacturer. The current evidence base is therefore of limited applicability to the Canadian decision making context.

Cost-effectiveness evidence suggests that well-designed independent analyses from the Canadian perspective are lacking; as a result, de novo modeling is required to address this evidence gap.

Appendix A1: Search Strategy

The following is the search strategy used in Ovid interfaces MEDLINE and EMBASE to identify health economic studies relating to pharmacologic treatments for OAB syndrome.

Embase Classic+Embase (1974 to 2015 August 18), **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations** (1946 to 2015 August 18)

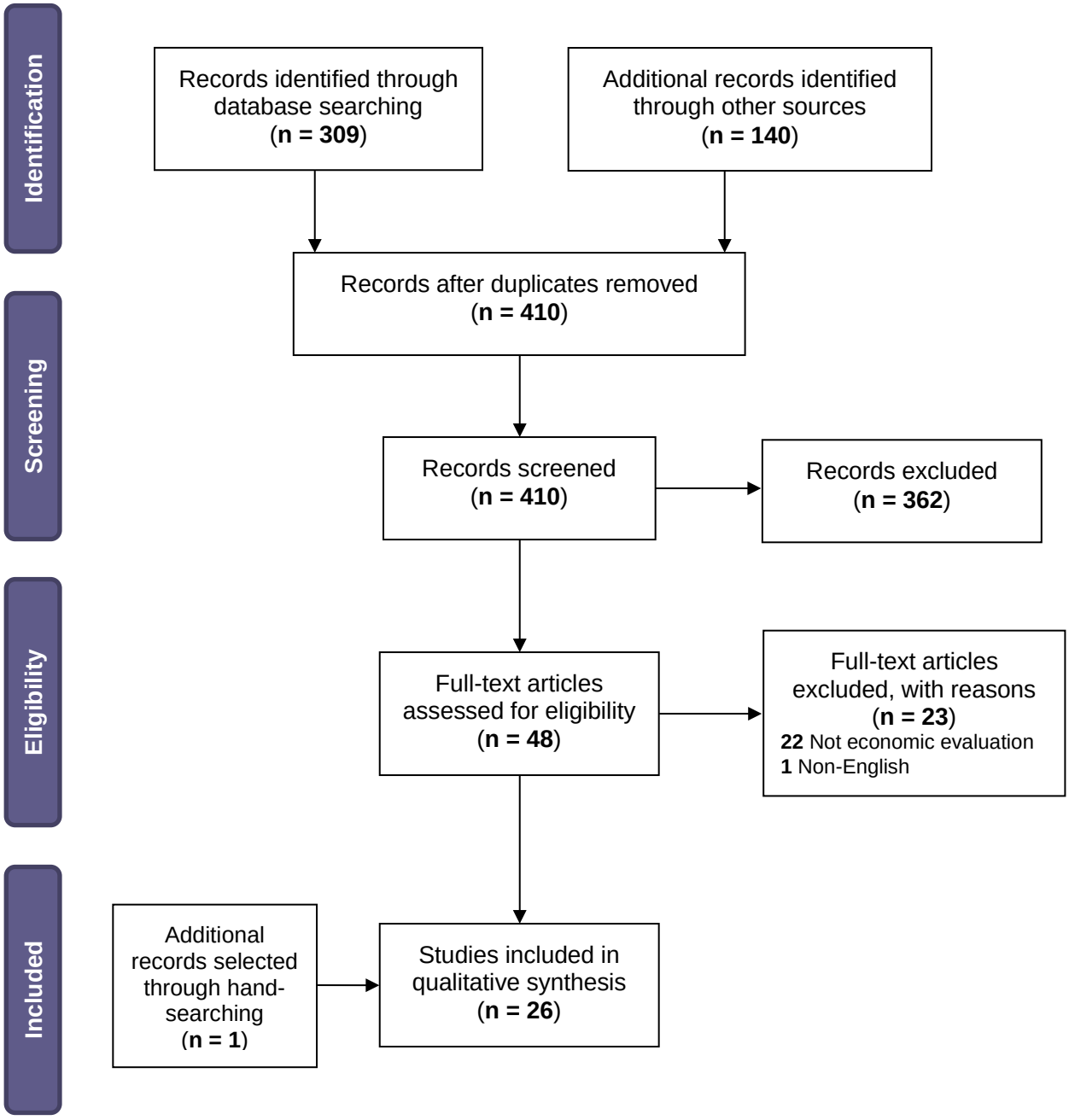
1 exp Urinary Bladder, Overactive/
2 exp Urinary Incontinence, Urge/
3 ((overactive adj2 (bladder* or detrusor*)) or (urina* adj2 (incontinen* or frequen*)) or (urge adj2 incontinen*) or (detrusor adj2 dyssynergia) or (bladder adj1 irritat*) or DESD).tw,kw.
4 or/1-3
5 exp Cholinergic Antagonists/
6 (((cholinergic* or acetylcholine) adj2 (antagonist* or blocker*)) or anticholinergic* or anti cholinergic* or AChR inhibitor* or cholinolytic*).tw,kw.
7 exp Muscarinic Antagonists/
8 ((muscarinic* adj2 (antagonist* or blocker*)) or antimuscarinic* or anti muscarinic* or muscarinolytic*).tw,kw.
9 Adrenergic beta-3 Receptor Agonists/
10 ((adrenergic adj1 (beta3 or "beta-3") adj2 agonist*) or (adrenoreceptor* adj1 (beta3 or "beta 3") adj2 agonist*) or (adrenergic adj2 receptor agonist*)).tw,kw.
11 (solifenacin or vesicare or vesikur or vesiker or vesitirim or ym53705 or "ym 53705" or ym905 or "ym 905").tw,kw.
12 (tolterodine or detrusitol or detrol or "detrol la" or pnu200583 or "pnu 200583" or unidet or urotrol).tw,kw.
13 (mirabegron or betanis or betmiga or myrbetique or sc211912 or "sc 211912" or YM178 or "YM-178").tw,kw.
14 (darifenacin or darifenacine or enablex or emselex or uk88525 or "uk 88525").tw,kw.
15 (fesoterodine or "spm 907" or spm907 or toviaz).tw,kw.
16 (oxybutynin or anturol or "apo-Oxybutynin" or contimin or cystonorm or cystrin or delifon or ditropan or diutropin or dresplan or dridase or driptane or esoxybutynin or frenurin or gelnique or "gen-oxybutynin" or iliaden or kentera or "kl 007" or kl007 or lenditro or "lyrinel XL" or "mutum cr" or nefryl or "novo-oxybutynin" or "nu-oxybutyn" or "oxyb AbZ" or oxyban or oxybugamma or oxybutinin or obuton or oxymedin or oyrobin or oxytrol or "PMS-oxybutynin" or pollakis* or renamel or reteven or ryol or spasyt or tavor or tropan or uricont or uroflax or urotrol or zatur).tw,kw.
17 (trospium or ceris or spasmolyt or trospi or uraplex or urato or regurin or flotros or sanctura or tropez or tosec or spasmex or "spasmo-lyt" or "spasmo-rhoival" or "spasmo-urgenin" or spasmolyt or spasmourgenin).tw,kw.
18 Flavoxate/
19 (flavoxate or "ak 123" or ak123 or baduson or bladderon or bladuril or cleanxate or "dw 61" or dw61 or flavate or "flavo-spa" or flavorin or fucotin or genurin or harnin or spagerin or spasdic or spasuret or tonlin or urispas or uronid or uropeace or uroxate or voxate or yungken).tw,kw.
20 or/5-19
21 4 and 20
22 exp Animals/ not (exp Animals/ and Humans/)
23 21 not 22
24 23 use pmrz
25 Economics/
26 exp "Costs and Cost Analysis"/

27 Value of Life/
28 exp Economics, Hospital/
29 Economics, Medical/
30 Economics, Nursing/
31 Economics, Pharmaceutical/
32 or/25-31
33 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
34 (expenditure$ not energy).ti,ab.
35 (value adj1 money).ti,ab.
36 budget$.ti,ab.
37 or/33-36
38 32 or 37
39 24 and 38
40 exp overactive bladder/ or exp detrusor dyssynergia/
41 exp urinary urgency/ or exp urge incontinence/
42 exp urinary frequency/
43 exp bladder irritation/
44 ((overactive adj2 (bladder* or detrusor*)) or (urina* adj2 (incontinen* or frequen*)) or (urge adj2 incontinen*) or (detrusor adj2 dyssynergia) or (bladder adj1 irritat*) or DESD).tw,kw.
45 or/40-44
46 exp cholinergic receptor blocking agent/
47 (((cholinergic* or acetylcholine) adj2 (antagonist* or blocker*)) or anticholinergic* or anti cholinergic* or AChR inhibitor* or cholinolytic*).tw,kw.
48 exp muscarinic receptor blocking agent/
49 ((muscarinic* adj2 (antagonist* or blocker*)) or antimuscarinic* or anti muscarinic* or muscarinolytic*).tw,kw.
50 exp beta 3 adrenergic receptor stimulating agent/
51 ((adrenergic adj1 (beta3 or "beta-3") adj2 agonist*) or (adrenoreceptor* adj1 (beta3 or "beta 3") adj2 agonist*) or (adrenergic adj2 receptor agonist*)).tw,kw.
52 exp solifenacin/
53 (solifenacin or vesicare or vesikur or vesiker or vesitirim or ym53705 or "ym 53705" or ym905 or "ym 905").tw,kw.
54 exp tolterodine/
55 (tolterodine or detrusitol or detrol or "detrol la" or pnu200583 or "pnu 200583" or unidet or urotrol).tw,kw.
56 exp mirabegron/
57 (mirabegron or betanis or betmiga or myrbetique or sc211912 or "sc 211912" or YM178 or "YM-178").tw,kw.
58 exp darifenacin/
59 (darifenacin or darifenacine or enablex or emselex or uk88525 or "uk 88525").tw,kw.
60 exp fesoterodine/
61 (fesoterodine or "spm 907" or spm907 or toviaz).tw,kw.
62 exp oxybutynin/
63 (oxybutynin or anturol or "apo-Oxybutynin" or contimin or cystonorm or cystrin or delifon or ditropan or diutropin or dresplan or dridase or driptane or esoxybutynin or frenurin or gelnique or "gen-oxybutynin" or iliaden or kentera or "kl 007" or kl007 or lenditro or "lyrinel XL" or "mutum cr" or nefryl or "novo-oxybutynin" or "nu-oxybutyn" or "oxyb AbZ" or oxyban or oxybugamma or oxybutinin or obuton or oxymedin or oyrobin or oxytrol or "PMS-oxybutynin" or pollakis* or renamel or reteven or ryol or spasyt or tavor or tropan or uricont or uroflax or urotrol or zatur).tw,kw.
64 exp trospium chloride/
65 (trospium or ceris or spasmolyt or trospi or uraplex or urato or regurin or flotros or

sanctura or tropez or tosec or spasmex or "spasmo-lyt" or "spasmo-rhoival" or "spasmo-urgenin" or spasmolyt or spasmourgenin).tw,kw.
66 exp flavoxate/
67 (flavoxate or "ak 123" or ak123 or baduson or bladderon or bladuril or cleanxate or "dw 61" or dw61 or flavate or "flavo-spa" or flavorin or fucotin or genurin or harnin or spagerin or spasdic or spasuret or tonlin or urispas or uronid or uropeace or uroxate or voxate or yungken).tw,kw.
68 or/46-67
69 45 and 68
70 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/
71 exp humans/ or exp human experimentation/ or exp human experiment/
72 70 not 71
73 69 not 72
74 73 use emez
75 health economics/
76 exp economic evaluation/
77 exp "health care cost"/
78 exp pharmacoeconomics/
79 or/75-78
80 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
81 (expenditure$ not energy).ti,ab.
82 (value adj2 money).ti,ab.
83 budget$.ti,ab.
84 or/80-83
85 79 and 84
86 74 and 85
87 39 or 86
88 limit 87 to yr="2000-Current"
89 remove duplicates from 88

Appendix A2: Results of Search

Exhibit 1: Flow diagram of the selection process for potentially relevant studies.



Appendix A3: List of Excluded Studies

Exhibit 2: List of excluded studies and reasons for exclusion

Study Reference	Reason for exclusion
Aballea S, Maman K, Desroziers K, Nazir J, Odeyemi IAO, Hakimi Z, et al. PUK21 - Cost-Effectiveness of Mirabegron Compared with Tolterodine ER 4mg for the Treatment of Patients with Overactive Bladder in the United Kingdom: Results from a Trial-Based Model [abstract]. Value in Health. 2013;16(7):A633. (Presented at ISPOR 16th Annual European Congress in Dublin, Ireland; 2013 Nov 2 - 2013 Nov 6).	Not economic evaluation
Angulo J, Rejas J, Linden K, Kvasz MG, Snedecor SJ. Cost-effectiveness of fesoterodine and tolterodine for the treatment of overactive bladder with urge urinary incontinence in Spain and Finland [abstract]. Value in Health. 2013;16(7):A633. (Presented at ISPOR 16th Annual European Congress in Dublin, Ireland; 2013 Nov 2 - 2013 Nov 6).	Not economic evaluation
Arreola-Ornelas H, Rosado-Buzzo A, Garcia-Mollinedo M, Camacho-Cordero L, Mucino-Ortega E, Mould-Quevedo JF, et al. Cost-effectiveness of tolterodine as treatment for overactive bladder (OAB) in adult mexican patients [abstract]. Value in Health. 2011;14(3):A76. (Presented at 16th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research in Baltimore, MD, United States; 2011 May 21 - 2011 May 25).	Not economic evaluation
Avksent'eva MV, Gerasimova KV, Khachatrian GR, Frolov MI, Omel'ianovskii VV, Avksent'ev NA. Pharmacoeconomic study of using solifenacin for the treatment of urge urinary incontinence in patients with overactive bladder syndrome. Urologiia. 2014;5(1):56-8-60-1.	Non-English
Blaser DA, Kohn MJ, Ousterhout M. Cost-effectiveness analysis of three months treatment with fesoterodine compared to generic oxybutynin extended-release in women with urinary incontinence from a third party payer perspective. [abstract]. Value in Health. 2010;13(3):A78-A79. (Presented at 15th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research in Atlanta, GA, United States; 2010 May 15 - 2010 May 19).	Not economic evaluation
Freemantle N, Khalaf K, Hepp Z, Ni Q, Fleetwood K, Stanisic S, et al. Cost-effectiveness of onabotulinumtoxinA vs. mirabegron for the treatment of overactive bladder from the UK national health perspective\ [abstract]. European Urology, Supplements. 2015;14(2):e151. (Presented at 30th Annual Congress of the European Association of Urology in Madrid, Spain; 2015 Mar 20 - 2015 Mar 24).	Not economic evaluation
Hart WM, Munro V, Retsa P. Cost-effectiveness analysis of solifenacin versus oxybutynin immediate-release in the treatment of patients with overactive bladder in the United Kingdom [abstract]. Value in Health. 2011;14(7):A332. (Presented at ISPOR 14th Annual European Congress in Madrid Spain; 2011 Nov 5 - 2011 Nov 8).	Not economic evaluation
Hart WM, Nazir J. Cost-effectiveness analysis of solifenacin succinate versus trospium chloride in the treatment of patients with overactive bladder in germany [abstract]. Value in Health. 2012;15(4):A156. (Presented at 17th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research in Washington, DC United States; 2012 Jun 2 - 2012 Jun 6).	Not economic evaluation

Study Reference	Reason for exclusion
Herschorn S, Vicente C, Nazir J, Ramos B, Hakimi Z. Cost-effectiveness of mirabegron 50mg compared to tolterodine er 4mg in the treatment of patients with overactive bladder in Canada [abstract]. Value in Health. 2014;17(7):A469. (Presented at ISPOR 17th Annual European Congress in Amsterdam, Netherlands; 2014 Nov 8 - 2014 Nov 12).	Not economic evaluation
Herschorn S, Vicente C, Piwko C. Cost-effectiveness of solifenacin versus oxybutynin immediate release for the treatment of patients with oveRactive bladder: Translating the VECTOR study results into pharmacoeconomic outcomes [abstract]. International Urogynecology Journal and Pelvic Floor Dysfunction. 2009;20(3 SUPPL.):S483. (Presented at 34th Annual Meeting of the International Urogynecological Association in Lago di Como, Italy; 2009 Jun 16 - 2009 Jun 20).	Not economic evaluation
Jo C, Lee SJ. An economic evaluation of fesoterodine in the treatment of overactive bladder (OAB) in Korea [abstract]. Value in Health. 2009;12(3):A200. (Presented at ISPOR 14th Annual International Meeting in Orlando, FL, United States; 2009 May 16 - 2009 May 20).	Not economic evaluation
Kelleher C, Aballea S, Maman K, Nazir J, Hakimi Z, Chambers C, et al. Cost effectiveness of solifenac in compared with oral antimuscarinic agents for the treatment of patients with overactive bladder (OAB) in the UK [abstract]. Value in Health. 2014;17(7):A469. (Presented at ISPOR 17th Annual European Congress in Amsterdam, Netherlands; 2014 Nov 8 - 2014 Nov 12).	Not economic evaluation
Lee R, Snedecor SJ, Kvasz MG, Trocio J, Borgman B. Updated economic analysis of fesoterodine relative to tolterodine and solifenacin for the treatment of overactive bladder: The swedish perspective [abstract]. Value in Health. 2011;14(3):A76. (Presented at 16th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research in Baltimore, MD, United States; 2011 May 21 - 2011 May 25).	Not economic evaluation
Malone DC, Armstrong EP, Bui C. Cost-effectiveness of pharmacologic treatment of overactive bladder [abstract]. Value in Health. 2012;15(4):A155. (Presented at 17th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research in Washington, DC United States; 2012 Jun 2 - 2012 Jun 6).	Not economic evaluation
Maman K, Neine M, Briquet B, Nazir J, Odeyemi IAO, Hakimi Z, et al. Cost-effectiveness of mirabegron compared with antimuscarinics for the treatment of patients with overactive bladder in the United Kingdom [abstract]. Value in Health. 2013;16(7):A633-A634. (Presented at ISPOR 16th Annual European Congress in Dublin, Ireland; 2013 Nov 2 - 2013 Nov 6).	Not economic evaluation
Posnett J, Walker A, Nazir J, Odeyemi IAO, Hakimi Z, Garnham A. Economic evaluation of pharmacological treatments for overactive bladder [abstract]. Value in Health. 2013;16(7):A633. (Presented at ISPOR 16th Annual European Congress in Dublin, Ireland; 2013 Nov 2 - 2013 Nov 6).	Not economic evaluation
Sanford M, Deng DY. Economics of Overactive Bladder. Current Bladder Dysfunction Reports. 2014;9(1):52-7.	Not economic evaluation
Schwartz EL, Hay JW. Cost-effectiveness analysis in treating overactive bladder with urge incontinence in women: A comparison between oxybutynin and tolterodine with exploratory analysis of fesoterodine [abstract]. Value in Health. 2010;13(3):A79. (Presented at 15th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research in Atlanta, GA, United States; 2010 May 15 - 2010	Not economic evaluation

Study Reference	Reason for exclusion
May 19).	
Warner JL. The cost-effectiveness of solifenacin vs fesoterodine, oxybutynin immediate-release, propiverine, tolterodine extended-release and tolterodine immediate-release in the treatment of patients with overactive bladder in the UK national health service. BJU International. 2010;106(4):586.	Not economic evaluation
Wielage RC, Perk S, Campbell NL, Ng D, Klein TM, Posta LM, et al. The cost effectiveness of mirabegron for the treatment of overactive bladder: Three us perspectives [abstract]. Journal of the American Geriatrics Society. 2015;63:S67. (Presented at 2015 Annual Scientific Meeting of the American Geriatrics Society in National Harbor, MD, United States; 2015 May 15 - 2015 May 17).	Not economic evaluation
Wu J, Siddiqui NY, Amundsen CL, Myers ER, Visco AG. A cost-effectiveness analysis of botulinum toxin a injection versus anticholinergic medications for the primary treatment of idiopathic urge incontinence [abstract]. Journal of Pelvic Medicine and Surgery. 2008;14(4):238-9. (Presented at 29th Annual Scientific Meeting of the American Urogynecologic Society in Chicago, IL, United States; 2008 Sep 4 - 2008 Sep 6).	Not economic evaluation
Xie J, Zhou ZY, Bui CN, Yan Y, De G, Runken MC, et al. Cost-effectiveness analysis of mirabegron versus tolterodine extended release in the treatment of patients with overactive bladder in the United States [abstract]. Value in Health. 2012;15(7):A457. (Presented at ISPOR 15th Annual European Congress in Berlin, Germany; 2012 Nov 3 - 2012 Nov 7).	Not economic evaluation
Zyczynski H. Comparison of cost-effectiveness of onabotulinumtoxin a and anticholinergic medications for the treatment of urgency urinary incontinence [abstract]. Neurourology and Urodynamics. 2013;32(6):720-1. (Presented at 43rd Annual Meeting of the International Continence Society in Barcelona, Spain; 2013 Aug 26 - 2013 Aug 30).	Not economic evaluation

Appendix A4: List of Included Studies

Exhibit 3: List of included studies within the review.

Reference #	Study Reference
1	Aballea S, Maman K, Thokagevistk K, Nazir J, Odeyemi IAO, Hakimi Z, et al. Cost Effectiveness of Mirabegron Compared with Tolterodine Extended Release for the Treatment of Adults with Overactive Bladder in the United Kingdom. Clinical Drug Investigation. 2014;35(2):83-93.
24	Angulo JC, Valpas A, Rejas J, Linden K, Kvasz M, Snedecor SJ. Cost effectiveness of fesoterodine and tolterodine for the treatment of overactive bladder with urge urinary incontinence in Spain and Finland. Clinical Drug Investigation. 2014;34(5):297-307.
10	Arikian SR, Casciano J, Doyle JJ, Tarride JE, Casciano RN. A pharmacoeconomic evaluation of two new products for the treatment of overactive bladder. Managed Care Interface. 2000;13(2):88-94.
23	Arlandis-Guzman S, Errando-Smet C, Trocio J, Arumi D, Rejas J. Cost-effectiveness analysis of antimuscarinics in the treatment of patients with overactive bladder in Spain: A decision-tree model. BMC Urology. 2011;11(9):1-11.
11	Armstrong EP, Malone DC, Bui CN. Cost-effectiveness analysis of anti-muscarinic agents for the treatment of overactive bladder. Journal of Medical Economics. 2012;15(Suppl 1):35-44.
2	Cardozo L, Thorpe A, Warner J, Sidhu M. The cost-effectiveness of solifenacin vs fesoterodine, oxybutynin immediate-release, propiverine, tolterodine extended-release and tolterodine immediate-release in the treatment of patients with overactive bladder in the UK National Health Service. BJU International. 2010;106(4):506-14.
3	Getsios D, Caro JJ, Ishak KJ, El-Hadi W, Payne K, O'Connel M, et al. Oxybutynin Extended Release and Tolterodine Immediate Release: A Health Economic Comparison. Clinical Drug Investigation. 2004;24(2):81-8.
16	Getsios D, Caro JJ, Ishak KJ, El-Hadi W, Payne K. Canadian economic comparison of extended-release oxybutynin and immediate-release tolterodine in the treatment of overactive bladder. Clinical Therapeutics. 2004;26(3):431-8.
25	Guest JF, Abegunde D, Ruiz FJ. Cost effectiveness of controlled-release oxybutynin compared with immediate-release oxybutynin and tolterodine in the treatment of overactive bladder in the UK, France and Austria. Clinical Drug Investigation. 2004;24(6):305-21.
4	Hakkaart L, Verboom P, Phillips R, Al MJ. The cost utility of solifenacin in the treatment of overactive bladder. International Urology and Nephrology. 2009;41(2):293-8.
5	Hart WM, Abrams P, Munro V, Retsa P, Nazir J. Cost-effectiveness analysis of solifenacin versus oxybutynin immediate-release in the treatment of patients with overactive bladder in the United Kingdom. Journal of Medical Economics. 2013;16(10):1246-54.
17	Herschorn S, Vicente C, Piwko C. Canadian cost-effectiveness analysis of solifenacin compared to oxybutynin immediate-release in patients with overactive bladder. Journal of Medical Economics. 2010;13(3):508-15.
6	Hughes DA, Dubois D. Cost-effectiveness analysis of extended-release formulations of oxybutynin and tolterodine for the management of urge incontinence. Pharmacoeconomics. 2004;22(16):1047-59.
12	Ko Y, Malone DC, Armstrong EP. Pharmacoeconomic evaluation of antimuscarinic agents for the treatment of overactive bladder. Pharmacotherapy. 2006;26(12):1694-702.
19	Kobelt G, Jonsson L, Mattiasson A. Cost-effectiveness of new treatments for overactive bladder: The example of tolterodine, a new muscarinic agent: A Markov model. Neurourology and Urodynamics. 1998;17(6):599-611.
26	Milsom I, Axelsen S, Kulseng-Hansen S, Mattiasson A, Nilsson CG, Wickstrom J. Cost-effectiveness analysis of solifenacin flexible dosing in patients with overactive bladder symptoms in four Nordic countries. Acta Obstetricia et Gynecologica Scandinavica. 2009;88(6):693-9.

Reference #	Study Reference
21	Nazir J, Hart WM. The cost-effectiveness of solifenacin vs. trospium in the treatment of patients with overactive bladder in the German National Health Service. Journal of Medical Economics. 2014;17(6):408-14.
9	Nazir J, Maman K, Neine M-E, Briquet B, Odeyemi IAO, Hakimi Z, et al. Cost-Effectiveness of Mirabegron Compared with Antimuscarinic Agents for the Treatment of Adults with Overactive Bladder in the United Kingdom. Value in Health. 2015;18(6):783-90.
7	Nazir J, Posnett J, Walker A, Odeyemi IA, Hakimi Z, Garnham A. Economic evaluation of pharmacological treatments for overactive bladder from the perspective of the UK National Health Service. Journal of Medical Economics. 2015;18(5):390-7.
20	Nilsson FOL, Linner L, Samuelsson E, Milsom I. Cost-effectiveness analysis of newer anticholinergic drugs for urinary incontinence vs oxybutynin and no treatment using data on persistence from the Swedish prescribed drug registry. BJU International. 2012;110(2):240-6.
13	Noe L, Becker R, Williamson T, Chen D. A pharmacoeconomic model comparing two long-acting treatments for overactive bladder. J Manage Care Pharm. 2002 Sep;8(5):343-52.
18	O'Brien BJ, Goeree R, Bernard L, Rosner A, Williamson T. Cost-effectiveness of tolterodine for patients with urge incontinence who discontinue initial therapy with oxybutynin: A Canadian perspective. Clinical Therapeutics. 2001;23(12):2038-49.
14	Perfetto EM, Subedi P, Jumadilova Z. Treatment of overactive bladder: A model comparing extended-release formulations of tolterodine and oxybutynin. American Journal of Managed Care. 2005;11(Suppl 4):S150-S157.
22	Pradelli L, Iannazzo S. Solifenacin in the treatment of overactive bladder syndrome in Italian patients: Pharmacoeconomic evaluation. Journal of Medical Economics. 2009;12(1):25-35.
8	Speakman M, Khullar V, Mundy A, Odeyemi I, Bolodeoku J. A cost-utility analysis of once daily solifenacin compared to tolterodine in the treatment of overactive bladder syndrome. Current Medical Research and Opinion. 2008;24(8):2173-9.
15	Wu JM, Siddiqui NY, Amundsen CL, Myers ER, Havrilesky LJ, Visco AG. Cost-Effectiveness of Botulinum Toxin A Versus Anticholinergic Medications for Idiopathic Urge Incontinence. Journal of Urology. 2009;181(5):2181-6.

Appendix A5: Characteristics of Reviewed Studies

Exhibit 4: Brief overview of included studies.

First author, Year	Country	Sponsorship	Study type	Model type	Time horizon	Included interventions
Aballea, 2014	UK	Astellas Pharma	CUA	Markov	5 years	MYR, TOL-ER, BTX
Angulo, 2014	Spain, Finland	Pfizer	CUA	Decision tree	1 year	FES, TOL-ER
Arikian, 2000	USA	Alza Corporation	CCA/CEA	Decision tree	6 months	OXY-ER, OXY-IR, TOL
Arlandis-Guzman, 2011	Spain	Pfizer	CUA	Decision tree	1 year	FES, TOL-ER, SOL
Armstrong, 2012	USA	Astellas	CEA	Decision tree	3 months	DAR, FES, OXY-IR, OXY-ER, OXY-TD gel, OXY-TD patch, SOL, TOL-IR, TOL-ER, TRO-IR, TRO-ER
Cardozo, 2010	UK	Astellas	CUA	Decision tree	1 year	FES, OXY-IR, PRO-ER, SOL, TOL-ER, TOL-IR
Getsios, 2004 Clin Drug Invest	UK	Janssen Pharmaceutica	CEA/CUA	Markov	1 year	OXY-ER, TOL-IR
Getsios, 2004 Clin Ther	Canada	Janssen-Ortho Canada	CEA	Markov	1 year	OXY-ER, TOL-IR
Guest, 2004	Austria, France, UK	Sanofi-Synthélabo	CEA	Decision tree	6 months	OXY-ER, OXY-IR, TOL-IR
Hakkart, 2009	UK	Yamanouchi Europe	CUA	Markov	1 year	SOL, placebo
Hart, 2013	UK	Astellas Pharma Europe Ltd.	CUA	Markov	1 year	SOL, OXY-IR
Herschorn, 2010	Canada	Astellas Pharma Canada Inc.	CUA	Markov	1 year	SOL, OXY-IR
Hugues, 2004	UK	Janssen Pharmaceutica	CEA	Decision tree	1 year	OXY-IR, OXY-ER, TOL-IR, TOL-ER

First author, Year	Country	Sponsorship	Study type	Model type	Time horizon	Included interventions
Ko, 2006	United States	Independent	CEA	Decision tree	3 months	OXY-IR, OXY-ER, OXY-TD patch, TOL-IR, TOL-ER, DAR, SOL, TRO
Kobelt, 1998	Sweden	Pharmacia & Upjohn	CEA/CUA	Markov	1 year	TOL-IR, no treatment
Milsom, 2009	Norway, Finland Sweden, Denmark	Astellas Denmark	CEA/CUA	Decision tree	1 year	SOL, TOL-ER, placebo
Nazir, 2014	Germany	Astellas Pharma Europe Ltd.	CUA	Markov	1 year	SOL, TRO
Nazir, 2015	UK	Astellas Pharma Europe Ltd.	CCA	Markov	1 year	Sequence A: OXY-ER, TOL-ER, SOL Sequence B: MYR, SOL, SOL
Nazir, 2015	UK	Astellas Pharma	CUA	Markov	5 years	MYR, TOL-ER, TOL-IR, SOL, FES, OXY-ER, OXY-IR, DAR, TRO
Nilsson, 2011	Sweden	Independent	CUA	Markov	1 year	OXY-IR, ACH, placebo, no treatment
Noe, 2002	USA	Pharmacia Corporation	CMA	Decision tree	3 months	OXY-ER, TOL-ER
O'Brien, 2001	Canada	Pharmacia Corporation	CEA / CUA	Markov	1 year	Strategy A: OXY, no treatment Strategy B: OXY, TOL
Perfetto, 2005	USA	Pfizer	CMA	Decision tree	1 year	OXY-ER, TOL-ER
Pradelli 2009	Italy	Astellas Pharma s.r.l.	CEA/CUA	Markov	1 year	SOL, TOL-ER, placebo, no treatment
Speakman, 2008	UK	Astellas Pharma Europe Ltd.	CUA	Markov	1 year	SOL, TOL-IR, TOL-ER
Wu, 2009	USA	None disclosed; pharma link	CUA	Markov	2 years	BTX, ACH

Note: ACH = anticholinergic medication (unspecified); BTX = botulinum toxin A injection; CCA = cost-consequence analysis; CEA = cost-effectiveness analysis; CMA = cost-minimization analysis; CUA = cost-utility analysis; DAR = darifenacin; ER = extended/controlled-release; FES = fesoterodine; IR = immediate-release MYR = mirabegron; OXY = oxybutynin; PRO = propiverine; SOL = solifenacin; TOL = tolterodine; TRO = trospium

Exhibit 5: Detailed characteristics of included studies.

First Author, Year	Aballea, 2014	Angulo, 2014	Arikian, 2000
Sponsorship	Astellas Pharma	Pfizer Ltd.	Alza Corporation
Country	UK	Spain & Finland	United States
Perspective	HCP	HCP	HCP
Study type	CUA	CUA	CCA/CEA
Comparators	Mirabegron 50 mg/day Tolterodine ER 4mg/day Botulinum toxin (BTX) injection (as 3rd line treatment only)	Fesoterodine 4 mg/day (8 mg/day titration at 4 weeks) Tolterodine ER 4 mg/day	Oxybutinin CR 15 mg/day Oxybutinin IR Tolterodine 4mg/day (6mg/day)
Target population	Adult patients with OAB syndrome	Individuals ≥18 years of age with OAB (i.e. eight or more micturitions/day, one or more UUI episode/day, and/or two or more urgency episodes/day).	Patients with OAB syndrome
Time horizon	5 years	1 year	6 months
Type of model	Markov	Decision tree	Decision tree
Adverse events	Included	Included	Not included
Results	Mirabegron streategy: Costs - £1,645.62 QALYs - 3.764 Tolterodine strategy: Costs - £1,607.75 QALYs - 3.755 Mirabegron was associated with a gain of 0.009 QALYs and an additional cost of £37.88 over the modeled 5-year period (ICER = £4,368/QALY gained). 1.00 £ = 1.59 CAD; 2012	Finnish perspective: Fesoterodine (€7,885; 0.7622 QALYs) dominated tolterodine (€8,024; 0.7559 QALYs) Spanish perspective: Fesoterodine - €15,633/QALY gained versus tolterodine ER 1.00 € = 1.32 CAD; 2012	• Tolterodine dominated by oxybutinin IR and oxybutinin CR • Oxybutinin CR - $1.24/success versus oxybutining IR • Oxybutinin CR - $0.76/continent day versus oxybutining IR • Initiating treatment with oxybutinin CR yielded the highest expected success rates and the highest number of expected continent days, as compared with tolterodine and oxybutinin IR; oxybutinin CR provided a lower cost alternative to tolterodine, and comparable cost to oxybutinin IR 1.00 USD = 1.53 CAD; 1999

First Author, Year	Arlandis-Guzman, 2011	Armstrong, 2012	Cardozo, 2010
Sponsorship	Pfizer	Astellas	Astellas
Country	Spain	United States	UK
Perspective	Societal	TPP	HCP
Study type	CUA	CEA	CUA
Comparators	Fesoterodine 4 mg/day Tolterodine ER 4 mg/day Solifenacin 5 mg/day	Darifenacin 7.5 mg/day Fesoterodine 8 mg/day Oxybutynin IR 5 mg BID Oxybutynin ER 30 mg/day Oxybutynin TD gel 1 sachet daily Oxybutynin TD patch every 3.5 days Solifenacin 5 mg/day Tolterodine IR 2 mg/day Tolterodine ER 4 mg/day Trospium IR 20 mg BID Trospium ER 60 mg/day	fesoterodine 4 mg/day & 8 mg/day oxybutynin IR 15 mg/day propiverine ER 20 mg/day solifenacin 5 mg/day & 10 mg/day tolterodine ER 4 mg/day tolterodine IR 2 mg/day and 4 mg/day
Target population	Patients (≥18 years) with OAB and incontinence	Patients with OAB syndrome	Patients with OAB syndrome (no symptom details provided).
Time horizon	1 year	3 months	1 year
Type of model	Decision tree	Decision tree	Decision tree
Adverse events	Included	Included	Not included
Results	Fesoterodine dominated tolterodine and solifenacin Fesoterodine QALY gain - 0.01014; solifenacin QALY gain – 0.00957; tolterodine QALY gain – 0.00846 Fesoterodine costs – €1,937; solifenacin costs – €1,960; tolterodine costs – €2,089 1.00 € = 1.51 CAD; 2010	Oxybutynin IR was least costly (and most cost-effective) All other treatment apart from solifenacin were dominated by solifenacin Solifenacin vs oxybutynin IR - $1338 per additional continent patient 1.00 USD = 1.00 CAD; 2010	• Oxybutynin IR was the least costly therapy • Fesoterodine, tolterodine ER & tolterodine IR dominated by solifenacin • Solifenacin - £80,000/QALY versus oxybutynin IR 1.00 £ = 2.28 CAD; 2007

First Author, Year	Getsios, 2004 Clin Drug Invest	Getsios, 2004 Clin Ther	Guest, 2004
Sponsorship	Janssen Pharmaceutica	Janssen-Ortho Canada	Sanofi-Synthélabo
Country	UK	Canada	Austria, France & UK
Perspective	HCP	HCP	Societal
Study type	CEA/CUA	CEA	CEA
Comparators	Oxybutynin ER 4 mg/day Tolterodine IR 4 mg/day	Oxybutynin ER 10 mg daily Tolterodine IR 2 mg BID	oxybutynin ER (up to 10 mg/day) oxybutynin IR (up to 10 mg/day) tolterodine IR (up to 4 mg/day)
Target population	Community-dwelling adults with urge or mixed urinary incontinence	Community-dwelling adults with OAB	Patients with OAB >18 years who had urge or mixed incontinence with a primary urge component
Time horizon	1 year	1 year	6 months
Type of model	Markov model	Markov model	Decision tree
Adverse events	Non included	Not included	Included
Results	Oxybutynin XL dominated tolterodine IR for all endpoints 1.00 £ = 2.32 CAD; 2002	Oxybutynin XL dominated tolterodine IR with 16.5 additional incontinent free days and one year cost of $32 lower than tolterodine IR	Oxybutynin CR was dominant therapy in UK and Austria and cost-effective in France (cost-effective in reducing the frequency of incontinence at 6 mos and in reducing micturition frequency at 6 mos)

First Author, Year	Hakkart, 2009	Hart, 2013	Herschorn, 2010
Sponsorship	Yamanouchi Europe	Astellas Pharma Europe Ltd.	Astellas Pharma Canada, Inc.
Country	UK	UK	Canada
Perspective	HCP	HCP	HCP
Study type	CUA	CUA	CUA
Comparators	Solifenacin 5 mg daily Solifenacin 10 mg daily Placebo	Solifenacin 5 mg/day (10 mg/day at 8 weeks) Oxybutynin IR 5 mg TID	Solifenacin 5 mg daily Oxybutynin IR 5 mg TID
Target population	Patients aged ≥18 years with symptoms of overactive bladder (including urinary frequency, urgency, or urge incontinence ≥3 episodes during a 3-day micturition diary) for more than 3 months and a micturition frequency of more than 8 times per 24hrs.	Patients with OAB syndrome	Patients with OAB syndrome (i.e. subjects with ≥1 urgency episode/24h (with or without urgency urinary incontinence) and ≥8 micturitions/24h for ≥3 months)
Time horizon	1 year	1 year	1 year
Type of model	Markov model	Markov model	Markov model
Adverse events	Not included	Not included	Included
Results	Solifenacin 5 mg versus placebo – ICER = £17,602/QALY Solifenacin 10 mg versus placebo ICER = £24,464/QALY 1.00 £ = 2.31 CAD; 2004	Solifenacin vs Oxybutynin (w/o incontinence pads) ICER=£15,093/QALY Solifenacin vs Oxybutynin (w/ incontinence pads) ICER=£12,309/QALY 1.00 £ = 1.70 CAD; 2010	Solifenacin vs Oxybutynin (w/o incontinence pads) ICER=$14,092/QALY Solifenacin vs Oxybutynin (w/ incontinence pads) Solifenacin is dominant

First Author, Year	Hugues, 2004	Ko, 2006	Kobelt, 1998
Sponsorship	Janssen Pharmaceutica	Independent	Pharmacia & Upjohn
Country	UK	United States	Sweden
Perspective	HCP	HCP	HCP
Study type	CEA	CEA	CEA/CUA
Comparators	Oxybutynin IR 5 mg TID Oxybutynin ER 10 mg daily Tolterodine IR 2 mg BID Tolterodine ER 4 mg daily	Oxybutynin IR 5 mg TID Oxybutynin ER 10 mg/day Oxybutynin TD patch 3.9 mg every 3-4 days Tolterodine IR 2 mg BID Tolterodine ER 4 mg/day Darifenacin 15 mg/day Solifenacin 5 mg/day Trospium 20 mg BID	Tolterodine IR 2 mg BID No treatment (no effect)
Target population	Patients with urge urinary incontinence.	Patients with OAB syndrome	Patients with OAB syndrome
Time horizon	1 year	3 months	1 year
Type of model	Decision tree	Decision tree	Markov model
Adverse events	Included	Included	Not included
Results	• Oxybutynin IR versus no treatment – £2.58 to £16.59 per incontinent free week • Tolterodine ER vs oxybutynin IR – £7.14 per incontinent free week • Oxybutynin XL vs tolterodine ER – £84.82 per incontinent free week • Tolterodine IR dominated by tolterodine ER 1.00 £ = 2.24 CAD; 2001	Solifenacin dominated all other antimuscarinic agents as they were all associated with high costs and low effectiveness 1.00 USD = 1.20 CAD; 2005	Tolterodine vs placebo: $23,032 per QALY Tolterodine vs placebo: $215 per additional month spent with minimal symptoms 1.00 USD = 1.43 CAD; 1997

First Author, Year	Milsom, 2009	Nazir, 2014	Nazir, 2015 J Med Econ
Sponsorship	Astellas Denmark	Astellas Pharma Europe Ltd.	Astellas Pharma Europe Ltd.
Country	Norway, Finland, Sweden and Denmark	Germany	UK
Perspective	Societal and HCP	HCP (German TPP)	HCP
Study type	CEA/CUA	CUA	CCA
Comparators	Solifenacin 5 mg/day and 10 mg/day (flexible dosing) Tolterodine ER 4 mg/day Placebo	Solifenacin 5 mg/day, 10 mg/day Trospium 20 mg BID Trospium 60 mg/day	Treatment sequence A (standard): 1st line: Oxybutynin ER 10 mg/day (generic) 2nd line: Tolterodine ER 4 mg/day (generic) 3rd line: Solifenacin 5 mg/day Treatment sequence B (new): 1st line: Mirabegron 50 mg/day 2nd line: Solifenacin 5 mg/day 3rd line: Solifenacin 10 mg/day
Target population	Patients with OAB symptoms	Patients with OAB syndrome	Patients with OAB aged ≥40 years and currently receiving anti-muscarinic therapy
Time horizon	1 year	1 year	1 year
Type of model	Decision tree	Markov model	Markov model
Adverse events	Included	Not included	Included
Results	• Solifenacin dominated tolterodine from societal and HCP perspectives • Solifenacin versus placebo – €14,318 to €27,603 per QALY, depending on country from societal perspective • Solifenacin versus placebo – €24,084 to €33,757 per QALY, depending on country from HCP perspective 1.00 € = 1.37 CAD; 2005	• Trospium 60 mg dominated by trospium 40 mg • Trospium 40 mg versus solifenacin 5 mg/ 10 mg - €19,893/QALY gained Solifenacin QALYs - 0.6857; Trospium 40 mg QALYs – 0.0.6802; Trospium 60 mg QALYs – 0.0.6800 Solifenacin costs – €970.01; Trospium 40 mg costs – €860.05; Trospium 60 mg costs – €875.05 1.00 € = 1.32 CAD; 2012	Standard treatment sequence (A): Patients controlled: 29.6 NNT to achieve one controlled patient: 33.8 Patients with no incontinence episodes per 24h: 103.6 Patients with <8 micturitions/24h: 228.7 Total costs = £1299/patient New treatment sequence (B) Patients controlled: 38.7 NNT to achieve one controlled patient: 25.8 Patients with no incontinence episodes per 24h: 123.7 Patients with <8 micturitions/24h: 262.1 Total costs = £1385/patient 1.00 £ = 1.59 CAD; 2012

First Author, Year	Nazir, 2015 Value Health	Nilsson, 2011	Noe, 2002
Sponsorship	Astellas Pharma	Independent	Pharmacia Corporation
Country	UK	Sweden	USA
Perspective	HCP	HCP	Societal
Study type	CUA	CUA	CMA
Comparators	Mirabegron 50 mg/day Tolterodine ER 4 mg/day Tolterodine IR 4 mg/day Solifenacin 5 or 10 mg/day Fesoterodine 4 or 8 mg/day Oxybutynin ER 10 mg/day Oxybutynin IR 10 or 15 mg/day Darifenacin 7.5 or 15 mg/day Trospium 60 mg/day	Oxybutynin IR 5 mg TID Newer anticholinergics as a group (solifenacin, tolterodine, fesoterodine, darifenacin and oxybutynin patch) No treatment (placebo effect) No treatment (no effect)	Oxybutynin ER 5 mg/day, 10 mg/day, 15 mg/day (flexible dosing) Tolterodine ER 2 mg/day and 4 mg/day (flexible dosing)
Target population	Adults patients with OAB syndrome	Patients who seek medical help due to frequency and urge incontinence.	Outpatients with a diagnosis of OAB seeking treatment from a primary care physician.
Time horizon	5 years	1 year	3 months
Type of model	Markov	Markov model	Decision tree
Adverse events	Included	Included	Not included
Results	In comparison with mirabegron 50 mg: Tolterodine ER 4 mg QALYs - 0.0104 Solifenacin 5 mg QALYs - 0.0045 Solifenacin 10 mg QALYs - 0.0105 Fesoterodine 4 mg QALYs - 0.0107 Fesoterodine 8 mg QALYs - 0.0123 Oxybutynin IR 10 mg QALYs - 0.0157 Oxybutynin ER 10 mg QALYs - 0.0135 Trospium 60 mg QALYs - 0.0097 Darifenacin 7.5 mg QALYs - 0.0132 Darifenacin 15 mg QALYs - 0.0172 Tolterodine ER 4 mg costs - £3,668.20 Solifenacin 5 mg costs - £12,856.57 Solifenacin 10 mg costs - £366.59 Fesoterodine 4 mg costs - £3,632.82 Fesoterodine 8 mg costs - £3,315.42 Oxybutynin IR 10 mg costs - £15,593.27 Oxybutynin ER 10 mg costs - £3,245.68 Trospium 60 mg costs - £8,647.29 Darifenacin 7.5 mg costs - £1,953.79 Darifenacin 15 mg costs - £3,887.14 1.00 £ = 1.59 CAD; 2012	• Newer anticholinergics versus no treatment – €21,045 / QALY • Newer anticholinergics versus placebo – €65,435 / QALY • Newer anticholinergics versus oxybutynin IR €37,119 / QALY 1.00 € = 1.51 CAD; 2010	Tolterodine ER – $1,207 for 3 months Oxybutynin CR - $1,283 for 3 months 1.00 USD = 1.45 CAD; 2000

First Author, Year	O'Brien, 2001	Perfetto, 2005	Pradelli 2009
Sponsorship	Pharmacia Corporation	Pfizer	Astellas Pharma s.r.l.
Country	Canada	US	Italy
Perspective	Societal	HCP	Societal and HCP
Study type	CEA / CUA	CMA	CEA/CUA
Comparators	Oxybutynin followed by no treatment in those who discontinue Oxybutynin followed by tolterodine 2 mg BID in those who discontinue	Oxybutynin ER 10 mg/day Tolterodine ER 4 mg/day	Solifenacin 5 mg/day Tolterodine ER 4 mg/day No treatment (placebo effect) No treatment (no effect)
Target population	Patients with urge incontinence who discontinue initial therapy with oxybutynin	Patients with OAB syndrome	Italian patients with OAB symptoms
Time horizon	1 year	1 year	1 year
Type of model	Markov model	Decision tree	Markov model
Adverse events	Not included	Not included	Not included
Results	Oxybutynin followed by tolterodine versus oxybutynin followed by no treatment : $9982 / QALY	Tolterodine ER - $8876 for 1 year Oxybutynin ER - $9080 for 1 year 1.00 USD = 1.29 CAD; 2004	Solifenacin vs placebo – €18,613/QALY Solifenacin vs no treatment – €7,634/QALY Tolterodine vs placebo – €2,600/QALY Tolterodine vs no treatment – €3,979/QALY Tolterodine dominated by solifenacin 1.00 GBP = 2.31 CAD; 2004

First Author, Year	Speakman, 2008	Wu, 2009
Sponsorship	Astellas Pharma Europe Ltd.	none disclosed; pharma link
Country	UK	United States
Perspective	HCP	HCP
Study type	CUA	CUA
Comparators	Solifenacin 5 mg/day and 10 mg/day (flexible dosing) Tolterodine IR 2 mg BID Tolterodine ER 4 mg/day	Botulinum toxin A (BoNT-A) injection Long-acting anticholinergic medication (unspecified)
Target population	Adults with OAB symptoms	Women in whom first line therapy with behavioural treatment and 1 anticholinergic medication failed (i.e. women with refractory idiopathic urge incontinence)
Time horizon	1 year	2 years
Type of model	Markov model	Markov model
Adverse events	Not included	Included (cost of complicatoins)
Results	Solifenacin was dominant treatment with lower costs versus tolterodine (£509 versus £526) and slightly greater QALY (difference of +0.04) 1.00 £ = 2.31 CAD; 2004	BoNT-A vs. anticholinergic regimen ICER = $14,377/QALY gained BoNT-A was more expensive than the anticholinergic regiment ($4,392 vs. $2,563), and was more effective at 1.63 vs. 1.50 QALYs. 1.00 USD = 1.00 CAD; 2008

Appendix B – De novo Economic Evaluation

Research Question

Based on a de novo economic model, what is the comparative cost-effectiveness of pharmacologic treatments for OAB syndrome?

Study Objectives

Based on the research question, the objectives of the study were to address the following specific question:

What is the cost effectiveness of initiating therapy for OAB with oxybutynin IR, oxybutynin ER, oxybutynin gel, oxybutynin transdermal, tolterodine IR, tolterodine ER, solifenacin, fesoterodine, trospium, darifenacin, or mirabegron, as compared with each other or no therapy?

Economic Evaluation

Model Structure

The costs and quality adjusted years (QALYs) associated with OAB therapies as compared with each other and no therapy were assessed using a Markov model. The results will be used to facilitate a discussion of the relative cost effectiveness of alternative reimbursement strategies for the coverage of OAB therapies. The therapies included in the comparison were oxybutynin IR, oxybutynin ER, oxybutynin gel, oxybutynin transdermal, tolterodine IR, tolterodine ER, solifenacin, fesoterodine, trospium, darifenacin and mirabegron.

In modelling disease progression in OAB, previous models have assessed disease severity by categorising patients by the number of micturitions per day and the number of incontinence episodes per day. Improvements in these symptoms have been demonstrated within one month of initiation of treatment and in some cases as early as seven days post initiation.[29,30] Most clinical trials are 3 months in duration with the improvement in symptoms at three months being at least equivalent to that seen at 1 month. There are few long term studies of OAB therapies and there is little information regarding the natural progression of the disease without treatment. Long term data derived from real world prescriptions claims databases shows that persistence with therapy is generally poor.[31,32] The primary reasons for discontinuing therapy include lack of response, side effects and improvement without medication.[30,33]

Given the limited data available with respect to long term efficacy and the natural history of the disease, estimating cost effectiveness over a period greater than three months requires a number of assumptions. Within the base case analysis, a 12 month time horizon was adopted using the efficacy data from the network meta-analysis in combination with real world data regarding compliance and treatment switching. Given the time horizon and that therapy does not impact mortality, mortality was not incorporated into the model. A shorter time horizon of 3 months, reflecting the time period over which clinical efficacy data is available for all therapies, was adopted within sensitivity analyses.

Within the model, a cohort of patients initiates therapy with one of the OAB therapies. With each one month cycle they either remain on first-line therapy or discontinue. Patients who

discontinue first-line therapy may either switch to an alternative second line therapy, with efficacy and side effects comparable to tolterodine ER, or not receive further OAB therapy. In those who do not receive further OAB therapy, OAB symptoms are assumed to resolve in a portion of patients and persist within the remaining patients. Patients whose OAB symptoms resolve are assumed to incur no further utility deficit or costs associated with OAB. In those patients who discontinue, but whose symptoms persist, they are assumed to incur the same costs and utility deficit as patients receiving no therapy with the same baseline symptoms. With each cycle patients may also discontinue second line therapy due to either resolution of symptoms or other reasons. For no therapy, the cohort of patients is assumed not to engage an alternative therapy for the full 12 months. Patients on no therapy can experience resolution of symptoms, which occurs with the same probability as with OAB treatment. A sensitivity analysis was conducted equating the efficacy and side effects of the second line therapy with solifenacin.

The states of the model were defined based on symptoms, specifically the number of micturitions in a 24 hour period and the number of incontinence episodes in a 24 hour period. The number of micturitions is grouped into five categories, as is the number of incontinence episodes. These together form the states of the model. Patients are assumed to begin at the mid-point of the respective level.

Exhibit 6: Definition of Micturition and Incontinence Symptom Levels*

Micturitions	
Level 1	8 or fewer episodes per 24 hours
Level 2	Greater than 8, but 10 or fewer episodes per 24 hours
Level 3	Greater than 10, but 12 or fewer episodes per 24 hours
Level 4	Greater than 12, but 14 or fewer episodes per 24 hours
Level 5	Greater than 14 episodes per 24 hours
Incontinence	
Level 1	Zero episodes per 24 hours
Level 2	Greater than 0, but 1 or fewer episodes per 24 hours
Level 3	Greater than 1, but 2 or fewer episodes per 24 hours
Level 4	Greater than 2, but 3 or fewer episodes per 24 hours
Level 5	Greater than 3 episodes per 24 hours

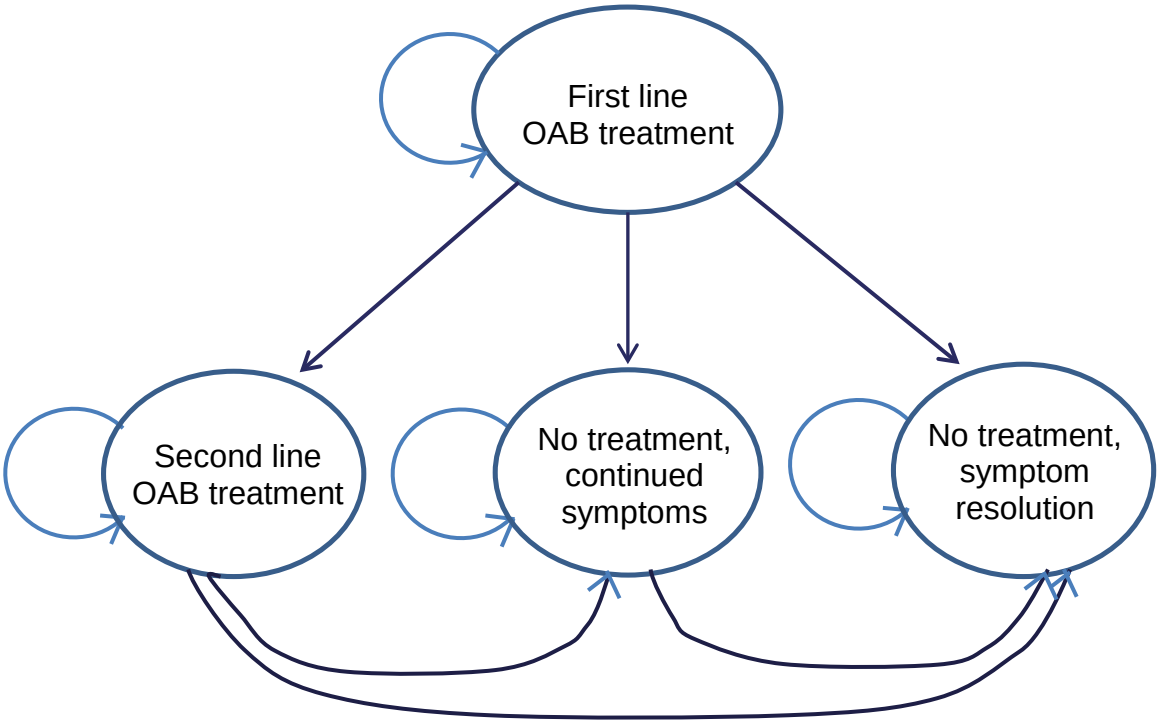
*Adapted from Aballea et al, 2015.[1]

Two approaches were taken for assessing the comparative cost effectiveness of treatments. In the first case, results were estimated for a cohort of patients entering the model with the same initial distribution of symptoms as patients at baseline, within a mirabegron clinical trial.[34] In the second case, a stratified analysis for each of the potential 24 combinations of symptom levels of micturitions and incontinence at initiation of therapy was conducted. Patients who remain on an OAB therapy experience a reduction in both micturition frequency and incontinence episodes as estimated within the accompanying network meta-analysis.

A frequent complaint of patients receiving therapy for OAB is with respect to their adverse effects which are often considered bothersome and may lead to discontinuation. Consequently, it is assumed that a portion of patients receiving therapy, which will differ based on the therapeutic agent, will experience adverse events with an associated disutility.

The cycle length is one month, with analysis conducted from the perspective of the healthcare system, with a sensitivity analysis from a societal perspective, including the cost of incontinence pads.

Exhibit 7: Schematic of 12-Month Markov Model



Footnote: A portion of patients receiving first line or second line OAB therapy experience adverse events, with treatment specific estimates sourced from the accompanying network meta-analysis. The distribution of the frequency of micturitions and incontinence episodes on first-line and second-line OAB therapy is derived from the accompanying network meta-analysis.

Data Inputs

Data Values

Data used within the economic model are provided in Appendix B1: Data Estimates. Details of data sources are provided below.

Initial Distribution of Symptom Severity

The base case analysis was conducted for a cohort of patients with OAB of varying severities. The baseline distribution of severity was derived from the baseline characteristics of patients within a mirabegron randomized controlled trial (Exhibit 8).[35]

Exhibit 8: Baseline distribution of symptoms of micturition and incontinence frequency*

Severity Level	Micturitions	Incontinence
1	6.30%	38.87%
2	30.69%	18.84%
3	27.18%	14.64%
4	19.46%	9.18%
5	16.37%	18.47%

*Adapted from Edwards et al., 2013.[35]

Stratified analysis was also conducted based on the 24 possible subgroups formed by the combination of each of the micturition levels in combination with each incontinence level (all possible combinations excluding level 1 for both micturitions and incontinence).

Treatment Effectiveness

For the first three months, in patients who remain on therapy, the improvement in symptoms was estimated from the companion network meta-analysis. The network meta-analysis provided the relative change from baseline in average number of micturitions and incontinence episodes over 24 hours at 3 months post initiation of therapy for OAB therapies versus placebo. Patients were assumed to be at the mid-point of the symptom level prior to initiation of therapy. The mean number of micturitions and incontinence episodes on therapies and for no therapy were calculated by adjusting the baseline numbers by the estimates of the mean decrease in the number of micturitions per day and incontinence episodes per day on each therapy. The distribution of patients across the symptom levels were estimated by assuming the symptom levels were normally distributed with the adjusted mean and a standard deviation based on the standard deviation of treatment effects within the placebo arms of the clinical trials. This allowed the estimation of the percentage of patients who would move to a lower or higher symptom level or remain at the same level, conditional upon their level at initiation.

Estimation of the effectiveness beyond 3 months requires a number of assumptions, as the majority of clinical trials are of 3 months duration or shorter. One would expect that those whose symptoms worsen on treatment would be more likely to discontinue treatment than those whose symptoms improved. Therefore, within the base case analysis, from 4 months onward, we assumed that those whose symptoms worsened would discontinue therapy and that those remaining on treatment would continue to experience the same benefits for subsequent months as they had during the first three months.

This assumption was tested within sensitivity analyses, by implementing two alternative approaches. In one case, the distribution of symptoms in those discontinuing therapy was assumed to not differ from those who continue therapy and in a second case, only those who improved by at least one symptom level remained on therapy.

Treatment Adverse Effects

The majority of treatments for OAB are anticholinergic therapies and therefore they are often associated with classic anticholinergic adverse effects including dry mouth and constipation. Estimates of the frequency of these adverse events with respect to each of the OAB therapies were derived from the companion network meta-analysis. Mirabegron, a newer OAB therapy,

is not an anticholinergic, but rather a beta-3 adrenergic agonist. It appears to be associated with fewer anticholinergic adverse effects than anticholinergic OAB therapies, but the overall rate of adverse events with mirabegron in long term trials was similar to tolterodine ER.[36] In the base case analysis the estimates from the network meta-analysis were used for all treatments, however, as the NMA only analyzed rates of dry mouth and constipation, in sensitivity analyses, the rate of adverse events with mirabegron was equated with that of tolterodine ER.

As with effectiveness, the data from the clinical trials provides an estimate of the frequency of adverse events within the first three months of treatment; however, one would expect that those who experience adverse effects that have a negative impact on their quality of life would be more likely to discontinue therapy. Additionally, if patients elect to continue therapy, even with adverse events, it is likely that the utility deficit of adverse events in these individuals is not significant. Therefore, within the base case analysis, we assumed that patients experienced adverse events at the rates estimated within the network meta-analysis for the first 3 months and that the probability of adverse events was zero for subsequent months. This reflects the assumption that those who experience adverse events either discontinue therapy by 3 months or that the adverse events they are experiencing are causing minimal negative impacts on quality of life. This was tested within sensitivity analyses by changing the assumption such that the distribution of adverse events does not differ between those who discontinue therapy and those who continue therapy.

Discontinuations

With each cycle of the model, a portion of patients discontinued therapy. The discontinuation rate was derived from analysis of Ontario prescription claims reflecting real world rates. (See Appendix B1: Data Estimates) Upon discontinuation of their initial OAB therapy, patients could either switch to an alternative OAB therapy (comparable to tolterodine ER) or discontinue OAB therapy. Estimates for the proportion of patients switching therapy were also derived from the prescription database. (See Appendix B1: Data Estimates) A portion of patients who switch to alternative therapy also discontinue this treatment each cycle. In those who discontinued OAB therapy, a portion of patients were assumed to have discontinued due to a resolution of symptoms and the remainder experienced the same benefit as those receiving no therapy (i.e. equal to that of no therapy). Based on a study by Benner, which investigated patient reported reasons for discontinuing OAB medications, 192 of the 5392 patients prescribed OAB therapies reported that they discontinued because their OAB symptoms had resolved.[30] This equates to 3.56% of patients resolving over a year, or a monthly probability of resolution of 0.003016. This value was tested within sensitivity analyses by reducing the percentage to 0% and doubling it.

As mirabegron has only been available for a short time in Canada, data regarding discontinuations was not available. The two most common reasons for discontinuation of OAB therapies are lack of efficacy and adverse events. Evidence suggests that the effectiveness of mirabegron is comparable to other OAB therapies; however, dry mouth and constipation, the two most common adverse effects of anticholinergic OAB therapies have been reported less frequently with mirabegron, at a rate comparable to placebo. Mirabegron, however, has been reported to increase blood pressure, and the overall rate of adverse events in a head to head clinical trial versus tolterodine ER was comparable between the two treatments.[36] Taking into account the available information regarding effectiveness and adverse events, within the base case, the discontinuation rate of mirabegron was equated to that of solifenacin, the anticholinergic OAB with the lowest discontinuation rate. This assumption was tested within sensitivity analyses.

Discontinuation rates were not available specific to tolterodine IR and tolterodine ER, and therefore the same discontinuation rate was used for both products. Additionally, three medications, oxybutynin ER, oxybutynin transdermal and oxybutynin gel are not covered by the provincial healthcare plan and therefore discontinuation rates were not available for these therapies. In the base case analysis, the discontinuation rates with these therapies was equated to that of tolterodine, which has a discontinuation rate lower than oxybutynin IR and trospium, but higher than solifenacin, fesoterodine and darafenacin.

These assumptions were tested within sensitivity analyses by increasing the discontinuation rates to that of trospium (the highest discontinuation rate, bar oxybutynin IR) and lowering it to that of solifenacin (the lowest discontinuation rate)).

Resource Use and Costs

Included within the model were the costs of medications and those of additional physician visits. In the base case analysis, the cost of incontinence pads was not incorporated as this expense is not borne by the public healthcare system; however, a sensitivity analysis was completed incorporating this cost.

For therapies covered by the Ontario Provincial Drug Plans (OPDP), the costs of medication were sourced from the Ontario Drug Benefit Formulary.[37] For therapies not covered by OPDP, wholesale prices were applied (Supplied by ODPRN through McKesson). The standard dispensing fee of $8.83 was applied four times per annum and a mark of up 8% was included. Based on these, a monthly drug cost was calculated and allocated to all patients on therapy at the start of each month.

Patients were assumed to visit their physician for an initial assessment and for regular follow up regardless of whether they received pharmacological therapy or supportive care and therefore these costs were not incorporated within the model.

Those receiving OAB specific drug therapies were assumed to incur the costs of a reassessment visit at all points where a treatment switch was made and at one month after initiation of any new OAB therapy. This assumption was tested within sensitivity analyses by removing the additional costs of the one month follow up visits. The cost of the physician visits was sourced from the Ontario Ministry of Health Schedule of Benefits.[38]

Incontinence pad usage, based on severity of incontinence, was sourced from a previous economic analysis which derived data from a mirabegron clinical trial.[1] (See Appendix B1: Data Estimates) An average representative retail cost per pad of $0.89 was sourced from a large Canadian retailer.[39]The extremes of high ($1.83) and low ($0.74) were tested within a sensitivity analysis.

Utilities

The impact of OAB symptoms on quality of life has been estimated using the EQ-5D. Data was collected during three 12 week RCTs which assessed the efficacy of mirabegron versus placebo. Information on both micturition and incontinence frequency was collected using a 3 day diary in addition to administration of the EQ-5D. Regression analysis was conducted which allows estimation of the disutility associated with each of the 5 levels of micturitions and the 5 levels of incontinence.[35] Age and gender were also included as covariates within the analysis. (Exhibit 9)

Exhibit 9: Coefficients for Estimation of Utility Values*

Variable	Level	Coefficient
Intercept		0.7838
Age		-0.00041
Micturition severity	1	0.06321
	2	0.04224
	3	0.02024
	4	0.01039
	5	0
Incontinence severity	1	0.05859
	2	0.04367
	3	0.03141
	4	0.01282
	5	0
Gender	Female	-0.04412
	Male	0

*Adapted from Edwards et al., 2013.[35]

The disutility associated with micturitions and that associated with incontinence episodes was shown to be independent within the analysis.

Two alternative sets of utility values derived from a different set of clinical trials using both the EQ-5D and the OAB-5D were used within sensitivity analyses.[40]

The disutility associated with adverse events was also taken into account. Based on a previous economic analysis, adverse events associated with OAB treatments are associated with an annual equivalent disutility of 0.0357. This value was converted to a monthly disutility of 0.00297 within the model. Alternative annual disutilities of 0 and 0.1 were used within sensitivity analyses.

Cost Effectiveness

For the cost utility analysis, costs and effects, as measured by quality adjusted life years (QALYs) gained associated with OAB treatments, are estimated via the model.

Given the 12 month duration of the model, costs and QALYs were not discounted.[41] The cost effectiveness of each of the treatments was estimated as the cost per quality adjusted life year gained relative to no therapy (placebo) and relative to the next most cost effective comparator treatment.

Deterministic Sensitivity Analyses

Due to the limited information regarding long term effectiveness and discontinuations with

OAB therapies and with respect to the natural history of OAB, a number of assumptions were required in developing the Markov model. To assess the impact of these assumptions on the results of the analysis, each assumption was tested within deterministic sensitivity analyses. The following table lists the assumptions incorporated within the model, the approach taken with the base case and the alternative assumptions tested within the sensitivity analysis.

Exhibit 10: Deterministic Sensitivity Analyses

	Base Case Assumption	Sensitivity Analysis: Alternate Assumption
Timing of discontinuation of therapy	Patients discontinue therapy at the end of the cycle	Patients discontinue therapy mid cycle
Symptoms in those discontinuing therapy	Patients whose symptoms worsen by 1 or more levels discontinue therapy	Patients whose symptoms don't improve by 1 or more levels discontinue therapy
Symptoms in those discontinuing therapy	Patients whose symptoms worsen by 1 or more levels discontinue therapy	Symptom distribution in those discontinuing therapy does not differ from those remaining on therapy
Adverse events in those remaining on therapy after 3 months	Adverse events in patients remaining on therapy after 3 months do not result in a utility deficit	Patients remaining on therapy after three months continue to experience adverse events with the same frequency and severity as within the first three months.
Physician visits	Patients are reassessed one months after initiating a new therapy and for treatment switches	Patients are only reassessed for treatment switches
Treatment discontinuation	Discontinuation rates with oxybutynin ER, oxybutynin transdermal, oxybutynin gel and tolterodine ER equated to that of tolterodine IR.	Discontinuation rates with oxybutynin ER, oxybutynin transdermal, oxybutynin gel and tolterodine ER equated to solifenacin (the lowest discontinuation rate) and to trospium (the highest discontinuation rate, except oxybutynin IR).
Treatment discontinuation	Discontinuation rate with mirabegron equated to solifenacin.	Discontinuation rate for mirabegron equated to trospium (the highest discontinuation rate, except oxybutynin IR) and reduced to half the rate of solifenacin.
Adverse events with mirabegron	Rates of dry mouth and constipation with mirabegron derived from network meta-analysis	Equated rates of mirabegron adverse events with that of tolterodine ER
Percent of people whose OAB symptoms resolve	3.56% annually	Reduced to a minimal value of 0% and increased to double the base value, 7.12%.
Utility values	Sourced from a large mirabegron clinical trial	Sourced from alternative study which pooled data from three large OAB clinical

	Base Case Assumption	Sensitivity Analysis: Alternate Assumption
	which collected symptom and quality of life data using the EQ-5D from OAB patients.	trials that collected symptom and quality of life data from OAB patients using both the EQ-5D and the OAB-5D
Utility values	Disutility associated with adverse drug reactions of -0.0357	Alternative disutility values of 0 and -0.1.
Costs of OAB therapies	Lowest available current price.	Alternative pricing of each therapy not currently available in generic form at 25% of the branded product. This would be the price of the product, provided at least three generic versions were available.
Costs of incontinence pad	Not included	Included at a standard cost sourced from a major retailer. Included at a lower and upper cost sourced from a major retailer.
Timeframe of the model	12 months	3 months
Alternative second line therapy	A therapy comparable to tolterodine ER was the second line therapy	A therapy comparable to solifenacin was the second line therapy

Probabilistic Sensitivity Analyses

A probabilistic sensitivity analysis was conducted in order to estimate the impact of parameter uncertainty on the cost effectiveness estimates. The parameters included within the PSA and their corresponding distributions are reported in Appendix B1: Data Estimates. A normal distribution was used for the mean change from baseline in symptoms and for disutilities. A beta distribution was used for the probability of discontinuation, treatment switch and developing adverse events.

The results of the PSA are presented through 95% credible interval around outcomes and by a cost effectiveness acceptability curve depicting the probability that each treatment option is the most cost effective at a range of threshold values for a QALY.

Findings

Base Case

Within the base case, the comparative cost effectiveness of OAB drug therapies and no therapy within a population of patients with OAB, whose distribution of symptom severity at baseline was assumed to be equivalent to that of a large clinical trial, was estimated. The results are reported for a cohort of 65 year old patients, 60% of which are female. Subgroup analysis was conducted for cohorts of patients with each of the possible 24 combinations of micturition and incontinence levels at baseline.

In the base case analysis, oxybutynin IR is the lowest cost alternative to no therapy, followed by solifenacin, both of which are available in generic form. (Exhibit 11) All other therapies are

more than double the cost of oxybutynin IR and solifenacin.

The increase in quality adjusted life years (QALYs) with treatments when compared with no therapy is small, with oxybutynin IR resulting in the smallest increase in QALYs and mirabegron, solifenacin and oxybutynin ER resulting in the greatest increases. In all cases, the difference from no therapy is less than 0.01 QALYs. In comparing the QALY gains with all treatments except oxybutynin IR, there was little difference between treatments with the range between the highest and lowest being 0.0027 QALYs.

Compared with no therapy, solifenacin results in the lowest ICER at $19,050 per QALY. In comparing other treatments with no therapy, oxybutynin IR would also be considered cost effective with an ICER of $27,442 per QALY and the ICERs for mirabegron ($51,197 per QALY), trospium ($53,171 per QALY) and fesoterodine ($56,168 per QALY) compared with no therapy are just higher than the frequently sited willingness to pay threshold of $50,000 per QALY.

In the sequential analysis, as solifenacin results in the greatest increase in QALYs at a lower cost than all alternatives except oxybutynin IR, it dominates all other treatments except oxybutynin IR, which is subject to extended dominance through solifenacin and no therapy.

Exhibit 11: Base Case Analysis

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.6836	$0.00	$0.00	$0.00
Solifenacin	0.6935	$187.78	$19,049.70	$19,049.70
Dominated				
Oxybutynin IR	0.6889	$145.36	$27,442.19	Subject to extended dominance through no therapy and Solifenacin
Mirabegron	0.6927	$464.08	$51,197.47	Dominated by Solifenacin
Trospium	0.6920	$442.69	$53,170.58	Dominated by Solifenacin
Fesoterodine	0.6915	$442.24	$56,168.19	Dominated by Solifenacin
Darifenacin	0.6909	$476.93	$65,456.58	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin ER	0.6934	$645.17	$66,168.22	Dominated by Solifenacin
Oxybutynin transdermal	0.6911	$524.62	$70,050.41	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin gel	0.6911	$553.56	$74,177.15	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal
Tolterodine ER	0.6909	$539.81	$74,531.85	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal
Tolterodine IR	0.6908	$539.74	$75,190.16	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal

Assumptions: those whose symptoms worsen on treatment discontinue therapy after 3 months.

Analysis by Patient Sub Populations

When separate analyses were conducted for cohorts of patients with each of the 24 combinations of micturition and incontinence symptom levels at baseline, the interpretation of the results was consistent with those of the base case (Exhibit 12). The ICER for solifenacin versus no therapy ranged from $13,900 to $32,800 per QALY. At all symptom levels,

oxybutynin IR was subjected to extended dominance through no therapy and solifenacin. All other treatments were either dominated by solifenacin or resulted in an ICER versus solifenacin greater than $400,000 per QALY.

When comparing each of the treatments with no therapy, at all symptom severity levels, oxybutynin IR resulted in an ICER of less than $50,000 per QALY, except in patients with baseline symptoms at level 1 for micturitions and level 5 for incontinence, where the ICER was $52,800 versus no therapy. In order of increasing ICER versus no therapy, solifenacin consistently had the lowest, generally followed by oxybutynin IR, mirabegron, fesoterodine, trospium and darifenacin with the ICERs generally falling between $40,000 and $60,000 per QALY. Typically, more treatments are potentially cost effective versus no therapy with increasing severity of symptoms, except when the highest symptom levels of micturitions (level 5) or incontinence (level 5) are reached. This is due to a combination of a floor effect, meaning that symptoms are so severe that any worsening of symptoms is not associated with worsening utilities and that the improvement in utilities between level 5 and level 4 is less than that seen when moving from level 4 to 3 or level 3 to 2.

Exhibit 12: Cost effectiveness of OAB therapies, by patient subgroup defined by micturition and incontinence levels at baseline

Symptom Category	ICER versus No therapy		Other Treatments
Micturition Level 1, Incontinence Level 2	Solifenacin	$23,337	ICER for mirabegron versus solifenacin: $1,852,497 Oxybutynin IR is subject to extended dominance through no therapy and solifenacin All other treatments are dominated by solifenacin
	Oxybutynin IR	$32,800	
	Mirabegron	$56,626	
	Fesoterodine	$65,439	
	Trospium	$67,117	
	Darifenacin	$73,444	
	Oxybutynin transdermal	$73,925	
	Tolterodine ER	$81,267	
	Oxybutynin gel	$82,853	
	Tolterodine IR	$83,935	
	Oxybutynin ER	$85,918	
Micturition Level 1, Incontinence Level 3	Solifenacin	$19,722	Oxybutynin IR is subject to extended dominance through no therapy and solifenacin All other treatments are dominated by solifenacin
	Oxybutynin IR	$26,995	
	Mirabegron	$49,160	
	Fesoterodine	$56,541	
	Trospium	$58,107	
	Darifenacin	$63,985	
	Oxybutynin transdermal	$64,198	
	Tolterodine ER	$70,924	
	Oxybutynin ER	$71,330	
	Oxybutynin gel	$72,434	
	Tolterodine IR	$73,049	
Micturition Level 1, Incontinence Level 4	Solifenacin	$19,389	Oxybutynin IR is subject to extended dominance through no therapy and solifenacin All other treatments are dominated by solifenacin
	Oxybutynin IR	$26,687	
	Mirabegron	$49,678	
	Fesoterodine	$57,701	
	Trospium	$58,848	
	Oxybutynin transdermal	$64,955	
	Darifenacin	$66,450	
	Oxybutynin ER	$68,471	
	Tolterodine ER	$72,821	
	Oxybutynin gel	$74,436	
	Tolterodine IR	$75,168	
Micturition Level 1, Incontinence Level 5	Solifenacin	$32,790	ICER for oxybutynin ER versus solifenacin: $853,920 Oxybutynin IR is subject to extended dominance through no therapy and solifenacin All other treatments are dominated by solifenacin
	Oxybutynin IR	$52,757	
	Mirabegron	$94,567	
	Oxybutynin ER	$103,025	
	Trospium	$115,519	
	Oxybutynin transdermal	$124,372	
	Fesoterodine	$124,815	
	Tolterodine ER	$158,580	

Symptom Category	ICER versus No therapy		Other Treatments
	Oxybutynin gel	$161,977	
	Darifenacin	$169,362	
	Tolterodine IR	$170,950	
Micturition Level 2, Incontinence Level 1	Solifenacin	$21,825	Oxybutynin IR is subject to extended dominance through no therapy and solifenacin All other treatments are dominated by solifenacin
	Oxybutynin IR	$31,213	
	Mirabegron	$54,513	
	Trospium	$59,321	
	Fesoterodine	$60,355	
	Darifenacin	$67,933	
	Oxybutynin transdermal	$73,278	
	Tolterodine ER	$77,444	
	Oxybutynin gel	$77,645	
	Tolterodine IR	$78,658	
	Oxybutynin ER	$79,748	
Micturition Level 2, Incontinence Level 2	Solifenacin	$17,880	Oxybutynin IR is subject to extended dominance through no therapy and solifenacin All other treatments are dominated by solifenacin
	Oxybutynin IR	$24,587	
	Mirabegron	$45,360	
	Trospium	$49,829	
	Fesoterodine	$50,074	
	Darifenacin	$56,497	
	Oxybutynin transdermal	$60,647	
	Tolterodine ER	$64,516	
	Oxybutynin ER	$64,752	
	Oxybutynin gel	$64,977	
	Tolterodine IR	$65,429	
Micturition Level 2, Incontinence Level 3	Solifenacin	$15,678	Oxybutynin IR is subject to extended dominance through no therapy and solifenacin All other treatments are dominated by solifenacin
	Oxybutynin IR	$21,174	
	Mirabegron	$40,440	
	Trospium	$44,684	
	Fesoterodine	$44,691	
	Darifenacin	$50,728	
	Oxybutynin transdermal	$53,942	
	Oxybutynin ER	$56,104	
	Tolterodine ER	$57,822	
	Oxybutynin gel	$58,390	
	Tolterodine IR	$58,619	
Micturition Level 2, Incontinence Level 4	Solifenacin	$15,467	Oxybutynin IR is subject to extended dominance through no therapy and solifenacin All other treatments are dominated by solifenacin
	Oxybutynin IR	$20,984	
	Mirabegron	$40,790	
	Trospium	$45,122	
	Fesoterodine	$45,413	
	Darifenacin	$52,265	
	Oxybutynin ER	$54,320	
	Oxybutynin transdermal	$54,476	
	Tolterodine ER	$59,077	
	Oxybutynin gel	$59,684	
	Tolterodine IR	$59,976	
Micturition Level 2, Incontinence Level 5	Solifenacin	$22,948	ICER for oxybutynin ER versus solifenacin: $856,182 Oxybutynin IR is subject to extended dominance through no therapy and solifenacin All other treatments are dominated by solifenacin
	Oxybutynin IR	$34,318	
	Mirabegron	$66,842	
	Trospium	$72,327	
	Oxybutynin ER	$74,014	
	Fesoterodine	$78,733	
	Oxybutynin transdermal	$90,893	
	Darifenacin	$100,114	
	Tolterodine ER	$105,253	
	Oxybutynin gel	$105,326	
	Tolterodine IR	$108,466	
Micturition Level 3, Incontinence Level 1	Solifenacin	$18,830	Oxybutynin IR is subject to extended dominance through no therapy and solifenacin All other treatments are dominated by solifenacin
	Oxybutynin IR	$27,227	
	Mirabegron	$49,675	
	Trospium	$49,963	
	Fesoterodine	$53,058	
	Darifenacin	$60,694	
	Oxybutynin ER	$66,905	
	Oxybutynin transdermal	$68,750	

Symptom Category	ICER versus No therapy		Other Treatments
	Oxybutynin gel	$69,931	
	Tolterodine ER	$70,764	
	Tolterodine IR	$70,775	
Micturition Level 3, Incontinence Level 2	Solifenacin	$15,818	Oxybutynin IR is subject to extended dominance through no therapy and solifenacin All other treatments are dominated by solifenacin
	Oxybutynin IR	$22,045	
	Mirabegron	$41,959	
	Trospium	$43,055	
	Fesoterodine	$44,946	
	Darifenacin	$51,399	
	Oxybutynin ER	$56,020	
	Oxybutynin transdermal	$57,512	
	Oxybutynin gel	$59,486	
	Tolterodine ER	$59,812	
	Tolterodine IR	$59,881	
Micturition Level 3, Incontinence Level 3	Solifenacin	$14,070	Oxybutynin IR is subject to extended dominance through no therapy and solifenacin All other treatments are dominated by solifenacin
	Oxybutynin IR	$19,261	
	Mirabegron	$37,715	
	Trospium	$39,159	
	Fesoterodine	$40,561	
	Darifenacin	$46,579	
	Oxybutynin ER	$49,429	
	Oxybutynin transdermal	$51,448	
	Oxybutynin gel	$53,918	
	Tolterodine ER	$54,015	
	Tolterodine IR	$54,127	
Micturition Level 3, Incontinence Level 4	Solifenacin	$13,900	Oxybutynin IR is subject to extended dominance through no therapy and solifenacin All other treatments are dominated by solifenacin
	Oxybutynin IR	$19,103	
	Mirabegron	$38,019	
	Trospium	$39,495	
	Fesoterodine	$41,155	
	Darifenacin	$47,872	
	Oxybutynin ER	$48,039	
	Oxybutynin transdermal	$51,933	
	Oxybutynin gel	$55,019	
	Tolterodine ER	$55,108	
	Tolterodine IR	$55,281	
Micturition Level 3, Incontinence Level 5	Solifenacin	$19,660	ICER for oxybutynin ER versus solifenacin: $636,524 Oxybutynin IR is subject to extended dominance through no therapy and solifenacin All other treatments are dominated by solifenacin
	Oxybutynin IR	$29,560	
	Trospium	$58,881	
	Mirabegron	$59,711	
	Oxybutynin ER	$62,822	
	Fesoterodine	$66,757	
	Oxybutynin transdermal	$84,028	
	Darifenacin	$85,147	
	Oxybutynin gel	$91,618	
	Tolterodine ER	$93,285	
	Tolterodine IR	$94,025	
Micturition Level 4, Incontinence Level 1	Solifenacin	$19,655	Oxybutynin IR is subject to extended dominance through no therapy and solifenacin All other treatments are dominated by solifenacin
	Oxybutynin IR	$29,143	
	Trospium	$51,772	
	Mirabegron	$52,694	
	Fesoterodine	$56,094	
	Darifenacin	$64,719	
	Oxybutynin ER	$68,980	
	Oxybutynin transdermal	$73,556	
	Oxybutynin gel	$74,293	
	Tolterodine IR	$75,401	
	Tolterodine ER	$75,530	
Micturition Level 4, Incontinence Level 2	Solifenacin	$16,397	Oxybutynin IR is subject to extended dominance through no therapy and solifenacin All other treatments are dominated by solifenacin
	Oxybutynin IR	$23,284	
	Mirabegron	$44,094	
	Trospium	$44,391	
	Fesoterodine	$47,105	
	Darifenacin	$54,256	
	Oxybutynin ER	$57,468	
	Oxybutynin transdermal	$60,838	

Symptom Category	ICER versus No therapy		Other Treatments
	Oxybutynin gel	$62,613	
	Tolterodine IR	$63,159	
	Tolterodine ER	$63,182	
Micturition Level 4, Incontinence Level 3	Solifenacin	$14,526	Oxybutynin IR is subject to extended dominance through no therapy and solifenacin All other treatments are dominated by solifenacin
	Oxybutynin IR	$20,200	
	Mirabegron	$39,431	
	Trospium	$40,262	
	Fesoterodine	$42,311	
	Darifenacin	$48,914	
	Oxybutynin ER	$50,553	
	Oxybutynin transdermal	$54,093	
	Oxybutynin gel	$56,474	
	Tolterodine ER	$56,748	
	Tolterodine IR	$56,791	
Micturition Level 4, Incontinence Level 4	Solifenacin	$14,344	ICER for oxybutynin ER versus solifenacin: $9,267,258 Oxybutynin IR is subject to extended dominance through no therapy and solifenacin All other treatments are dominated by solifenacin
	Oxybutynin IR	$20,027	
	Mirabegron	$39,763	
	Trospium	$40,617	
	Fesoterodine	$42,958	
	Oxybutynin ER	$49,099	
	Darifenacin	$50,342	
	Oxybutynin transdermal	$54,629	
	Oxybutynin gel	$57,683	
	Tolterodine ER	$57,956	
	Tolterodine IR	$58,063	
Micturition Level 4, Incontinence Level 5	Solifenacin	$20,562	ICER for oxybutynin ER versus solifenacin: $539,776 Oxybutynin IR is subject to extended dominance through no therapy and solifenacin All other treatments are dominated by solifenacin
	Oxybutynin IR	$31,832	
	Trospium	$61,410	
	Mirabegron	$64,128	
	Oxybutynin ER	$64,648	
	Fesoterodine	$71,634	
	Oxybutynin transdermal	$91,321	
	Darifenacin	$93,286	
	Oxybutynin gel	$99,252	
	Tolterodine ER	$101,749	
	Tolterodine IR	$102,368	
Micturition Level 5, Incontinence Level 1	Solifenacin	$26,469	Oxybutynin IR is subject to extended dominance through no therapy and solifenacin All other treatments are dominated by solifenacin
	Oxybutynin IR	$42,832	
	Trospium	$69,418	
	Mirabegron	$71,646	
	Fesoterodine	$77,903	
	Oxybutynin ER	$91,367	
	Darifenacin	$91,912	
	Oxybutynin transdermal	$101,079	
	Oxybutynin gel	$102,638	
	Tolterodine ER	$105,125	
	Tolterodine IR	$105,661	
Micturition Level 5, Incontinence Level 2	Solifenacin	$20,880	Oxybutynin IR is subject to extended dominance through no therapy and solifenacin All other treatments are dominated by solifenacin
	Oxybutynin IR	$31,269	
	Mirabegron	$56,628	
	Trospium	$56,763	
	Fesoterodine	$61,582	
	Darifenacin	$72,152	
	Oxybutynin ER	$72,207	
	Oxybutynin transdermal	$78,521	
	Oxybutynin gel	$81,607	
	Tolterodine ER	$82,645	
	Tolterodine IR	$83,092	
Micturition Level 5, Incontinence Level 3	Solifenacin	$17,938	ICER for oxybutynin ER versus solifenacin: $181,984,436 Oxybutynin IR is subject to extended dominance through no therapy and solifenacin All other treatments are dominated by solifenacin
	Oxybutynin IR	$25,949	
	Mirabegron	$49,162	
	Trospium	$50,182	
	Fesoterodine	$53,638	
	Oxybutynin ER	$61,617	
	Darifenacin	$63,002	
	Oxybutynin transdermal	$67,636	

Symptom Category	ICER versus No therapy		Other Treatments
	Oxybutynin gel	$71,479	
	Tolterodine ER	$71,971	
	Tolterodine IR	$72,410	
Micturition Level 5, Incontinence Level 4	Solifenacin	$17,662	ICER for oxybutynin ER versus solifenacin: $2,109,673 Oxybutynin IR is subject to extended dominance through no therapy and solifenacin All other treatments are dominated by solifenacin
	Oxybutynin IR	$25,664	
	Mirabegron	$49,679	
	Trospium	$50,734	
	Fesoterodine	$54,681	
	Oxybutynin ER	$59,471	
	Darifenacin	$65,391	
	Oxybutynin transdermal	$68,477	
	Oxybutynin gel	$73,428	
	Tolterodine ER	$73,926	
	Tolterodine IR	$74,491	
Micturition Level 5, Incontinence Level 5	Solifenacin	$28,139	ICER for oxybutynin ER versus solifenacin: $450,710 Oxybutynin IR is subject to extended dominance through no therapy and solifenacin All other treatments are dominated by solifenacin
	Oxybutynin IR	$48,904	
	Oxybutynin ER	$83,918	
	Trospium	$87,918	
	Mirabegron	$94,572	
	Fesoterodine	$111,495	
	Oxybutynin transdermal	$137,957	
	Oxybutynin gel	$157,279	
	Darifenacin	$162,648	
	Tolterodine ER	$163,913	
	Tolterodine IR	$167,490	

Deterministic Sensitivity Analysis

One-way sensitivity analyses found the results to be robust to alternative modelling assumptions with solifenacin remaining the most cost effective treatment as compared with no therapy in all scenarios. Solifenacin continued to either dominate other treatments, or they were subjected to extended dominance. In rare cases where alternative treatments resulted in greater QALYs than solifenacin, the alternative therapy was more expensive and resulted in an ICER in excess of $240,000 versus solifenacin (Appendix X).

Changing the assumptions did however change the relative cost effectiveness of treatments as compared with no therapy. The following table summarizes the findings of the sensitivity analyses.

Exhibit 13: Summary of Findings from Sensitivity Analysis

Assumption	Findings
Timing of discontinuation of therapy	Changing the timing of discontinuations to the middle of the cycle rather than the end of the cycle did not significantly affect the results.
Symptoms in those discontinuing therapy	In the base case, patients whose symptoms worsen by 1 or more levels discontinue therapy If patients who discontinued therapy after 3 months were assumed to have the same symptom distribution as those continuing on therapy, the ICER for solifenacin increased to $30,095 per QALY and the ICER for all other treatments versus no therapy exceeded $50,000 per QALY. If patients whose symptoms did not improve by at least one level were assumed to discontinue therapy after 3 months, the ICER for solifenacin versus no therapy improved to $13,354 per QALY and the ICER for all other treatments versus no therapy reduced to less than $50,000 per QALY. Solifenacin

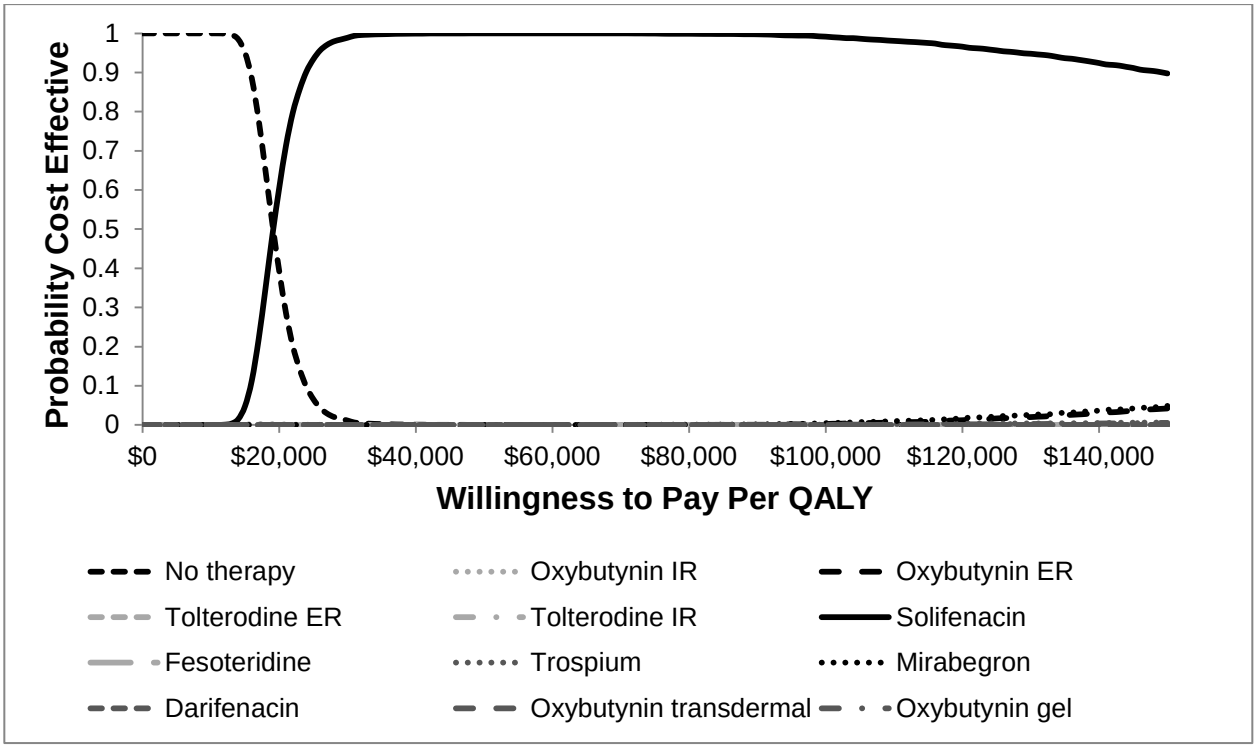
Assumption	Findings
	remained the most cost effective therapy dominating all other treatments or subjecting them to extended dominance.
Adverse events in those remaining on therapy after 3 months	Assuming that the frequency and severity of adverse events in those discontinuing therapy didn't differ from those remaining on therapy after 3 months did not significantly affect the results.
Physician visits	When patients were assumed to incur the cost of a reassessment visit only at times of treatment switches, solifenacin remained the most cost effective therapy versus no therapy with an ICER of $15,304 per QALY. All other treatments were dominated by solifenacin or subjected to extended dominance. The ICER for oxybutynin IR, mirabegron and trospium versus no therapy decreased such that they were below $50,000 per QALY being $20,494, $47,043 and $48,813, respectively.
Treatment discontinuation	Varying assumptions regarding the discontinuation rates with oxybutynin ER, oxybutynin transdermal, oxybutynin gel and tolterodine ER to extremes did not affect the results of the analysis. Increasing the discontinuation rate with mirabegron did not affect the results; however, decreasing the discontinuation rate to half that of solifenacin reduced the ICER for mirabegron versus no therapy to $47,986 per QALY. Solifenacin remained a less costly alternative with an ICER for mirabegron versus solifenacin of $240,390 per QALY.
Adverse events with mirabegron	Assuming that the frequency of adverse events with mirabegron is equivalent to the frequency with tolterodine ER did not significantly alter the results.
Percent of people whose OAB symptoms resolve	Changing the assumptions regarding the percentage of patients whose OAB symptoms resolve throughout the year from the extremes of 0% to 7.12% did not significantly affect the results.
Utility values	Incorporating alternative utility values based on Desrozier, elicited using the EQ-5D, did not significantly alter the results. Incorporating alternative utility values based on Desrozier, elicited using the OAB-5D, reduced the ICER for all treatments versus no therapy; however, solifenacin continued to dominate (or extendedly dominate) all treatments. The ICER for solifenacin versus no therapy is $13,571 per QALY. For all other treatments the ICER versus no therapy ranged from a low of $18,549 with oxybutynin IR to a high of $53,347 with tolterodine IR.
Disutility associated with adverse events	Incorporating alternative disutility values of 0 and -0.1 did not significantly affect the results.
Costs of OAB therapies	Assuming the availability of at least three generically equivalent products and a corresponding 25% reduction in the price of darifenacin, oxybutynin ER, oxybutynin transdermal, oxybutynin gel, tolterodine ER, and fesoterodine resulted in a decrease in the ICER for each of the products versus no therapy; however, solifenacin remained the most cost effective treatment option dominating the other treatments. Assuming this reduction in price with trospium, the ICER for trospium versus no

Assumption	Findings
	therapy of $18,774, whilst the ICER for solifenacin versus trospium is $20,549 per QALY. Thus, solifenacin remained the more cost effective treatment option. Assuming this reduction in price of mirabegron resulted in an ICER for mirabegron versus no therapy of $18,151. The ICER for solifenacin versus mirabegron is $29,326 per QALY. Thus, solifenacin remained the more cost effective treatment option.
Costs of incontinence pads	When the cost of incontinence pads was incorporated within the analysis the cost effectiveness of all treatments versus no therapy improved; however, solifenacin remained the most cost effective therapy dominating (or extendedly dominating) all other treatments with an ICER of $10,012 per QALY versus no therapy. The ICERs for oxybutynin IR, mirabegron, trospium and fesoterodine as compared with no therapy were also less than $50,000 per QALY at $16,161, $42,259, $45,085 and $47,125, respectively. The results did not change significantly when the extremes of a low and high cost incontinence pad were incorporated.
Timeframe of model	When the timeframe of the model was reduced from 12 months to 3 months the ICERs for treatments versus no therapy all increased; however, solifenacin remained the most cost effective treatment option with an ICER of $46,132 per QALY. The ICER for all other treatments versus no therapy increased to greater than $100,000 per QALY.
Alternative second line therapy	Assuming an alternative second line therapy, solifenacin, rather than tolterodine ER did not significantly affect the results. All therapies continued to be dominated or subjected to extended dominance by solifenacin or solifenacin and no therapy. The ICER for solifenacin versus no therapy is $17,678 per QALY. Both oxybutynin IR and mirabegron resulted in ICER below $50,000 per QALY at $19,246 and $48,721 per QALY, respectively.

Probabilistic Sensitivity Analysis

The results of the Monte Carlo Simulation are presented below. At willingness to pay values lower than $20,000 per QALY, no therapy had the highest probability of being the optimal therapy; whereas, at values greater than $20,000 solifenacin had the highest probability of being the optimal therapy. At a willingness to pay value of $50,000 solifenacin was the most cost effective therapy in 100% of replications.

Exhibit 14: Cost Effectiveness Acceptability Curve for OAB Therapies



Overall Summary

In comparing the cost effectiveness of drug therapies for OAB, solifenacin was found to be the most cost effective therapy. As compared with no therapy, the ICER for oxybutynin IR was lower than with solifenacin versus no therapy; however, it was extendedly dominated by no therapy and solifenacin. Given its cost effectiveness and significantly lower cost of generic solifenacin versus other branded OAB therapies, it would seem appropriate to initiate therapy with solifenacin. However, as the tolerability with OAB therapies is generally, low leading to high discontinuation rates, patients often try more than one therapy. Depending on the assumptions regarding the treatment approach, a number of the other OAB drug therapies may also be considered cost effective as compared with no therapy, although they are generally dominated by solifenacin. In patients who do not tolerate solifenacin, other OAB drug therapies may be cost effective alternatives as compared with no therapy and could be considered for second line therapy.

Conclusions

The results of this analysis show that solifenacin is the most cost effective therapy for the treatment of OAB. The generic price of solifenacin is considerably lower than other branded products, offering potential savings in the treatment of OAB. Given the high discontinuation rates with all OAB therapies, many patients will go on to alternative treatments after solifenacin. Oxybutinin IR may be a cost effective therapy in patients discontinuing solifenacin. Mirabegron, trospium and fesoterodine may be cost effective in patients discontinuing both solifenacin and oxybutynin IR if restricted to specific patient subgroups based on symptom levels. Darifenacin, oxybutynin ER, transdermal oxybutynin, oxybutynin gel, tolterodine ER and tolterodine IR are not cost effective based on a commonly used threshold of $50,000 per QALY gained.

Appendix B1: Data Estimates

Exhibit 15: Model inputs for base-case analysis with ranges for probabilistic sensitivity analysis

Input	Description	Value (SE/95% CI)	Distribution	Source
Disutility due to OAB Symptoms				
Micturition severity level	Level 1 Level 2 Level 3 Level 4 Level 5	0 -0.02097 (0.012384) -0.04279 (0.012183) -0.05282 (0.012183) -0.06321 (0.009100)	Normal Normal Normal Normal Normal	[1]
Incontinence severity level	Level 1 Level 2 Level 3 Level 4 Level 5	0 -0.01492 (0.011809) -0.02718 (0.012097) -0.04577 (0.012540) -0.05859 (0.008300)	Normal Normal Normal Normal Normal	[1]
Resource Usage				
Incontinence pads (number of pads per day)	0 >0 – 1 >1 – 2 >2 – 3 >3	0.17 (0.150 – 0.198) 0.75 (0.687 – 0.817) 1.38 (1.282 – 1.486) 1.89 (1.745 – 2.039) 3.34 (3.167 – 3.511)	Gamma Gamma Gamma Gamma Gamma	[1]
Physician Visits	Reassessment visits with all OAB treatments	reassessment visit at one month post initiation of new OAB therapy, one visit at treatment switch	Fixed	Assumed
Costs				
Drug costs per cycle	Oxybutynin IR Oxybutynin ER Oxybutynin transdermal Oxybutynin gel Tolterodine IR Tolterodine ER Darifenacin Solifenacin Trospium Fesoterodine Mirabegron	$9.43 $82.66 $65.28 $69.45 $67.46 $67.47 $55.88 $16.82 $55.92 $52.22 $50.90	Fixed	[37,42]
Physician visits	Follow-up consultation	$38.35	Fixed	[38]
Incontinence pad	Cost per pad	$0.89	Fixed	[39]
Relative Treatment Effects				
Change from baseline with no therapy	Micturitions Incontinence	-1.4636 (0.0713) -1.2984 (0.0831)	Normal Normal	Companion network meta-analysis
Mean change versus placebo in micturitions per 24 hours at one month	Oxybutynin IR Oxybutynin ER Oxybutynin transdermal Oxybutynin gel Tolterodine IR Tolterodine ER Darifenacin Solifenacin Trospium Fesoterodine Mirabegron	-0.7309 (0.1972) -1.1570 (0.2339) -0.4936 (0.2548) -0.6954 (0.2762) -0.6815 (0.1215) -0.6142 (0.0710) -0.7050 (0.2152) -0.9681 (0.0949) -1.0850 (0.3313) -0.8084 (0.0755) -0.6729 (0.0870)	Normal Normal Normal Normal Normal Normal Normal Normal Normal Normal Normal	Companion network meta-analysis
Mean change versus placebo in incontinence episodes per 24 hours at one month	Oxybutynin IR Oxybutynin ER Oxybutynin transdermal Oxybutynin gel Tolterodine IR Tolterodine ER Darifenacin Solifenacin Trospium	-0.6792 (0.1620) -0.9756 (0.1877) -0.4924 (0.2411) -0.3684 (0.2599) -0.3653 (0.0999) -0.3767 (0.0626) -0.3090 (0.1272) -0.7444 (0.0820) -0.4810 (0.2653)	Normal Normal Normal Normal Normal Normal Normal Normal Normal	Companion network meta-analysis

Input	Description	Value (SE/95% CI)	Distribution	Source
	Fesoterodine	-0.4323 (0.0669)	Normal	
	Mirabegron	-0.5103 (0.0932)	Normal	
Discontinuations, Treatment Switches and Adverse Events				
Monthly probability of discontinuation				ODPRN analysis of claims Equated to tolterodine IR
	Oxybutynin IR	0.1716 (0.0038)	Beta	Equated to tolterodine IR
	Oxybutynin ER	0.1072 (0.0433)	Beta	Equated to tolterodine IR
	Oxybutynin transdermal	0.1072 (0.0433)	Beta	ODPRN analysis of claims
	Oxybutynin gel	0.1072 (0.0433)	Beta	Equated to tolterodine IR
	Tolterodine IR	0.1072 (0.0433)	Beta	ODPRN analysis of claims
	Tolterodine ER	0.1072 (0.0433)	Beta	ODPRN analysis of claims
	Darifenacin	0.0955 (0.0057)	Beta	ODPRN analysis of claims
	Solifenacin	0.0815 (0.0023)	Beta	ODPRN analysis of claims
	Trospium	0.1105 (0.0158)	Beta	Equated to solifenacin
	Fesoterodine	0.0951 (0.0059)	Beta	
	Mirabegron	0.0815 (0.0038)	Beta	
Proportion of discontinuations switching to alternative OAB treatment				ODPRN analysis of claims Equated to tolterodine IR
	Oxybutynin IR	0.1766 (0.0038)	Beta	Equated to tolterodine IR
	Oxybutynin ER	0.1350 (0.0479)	Beta	Equated to tolterodine IR
	Oxybutynin transdermal	0.1350 (0.0479)	Beta	ODPRN analysis of claims
	Oxybutynin gel	0.1350 (0.0479)	Beta	Equated to tolterodine IR
	Tolterodine IR	0.1350 (0.0479)	Beta	ODPRN analysis of claims
	Tolterodine ER	0.1350 (0.0479)	Beta	ODPRN analysis of claims
	Darifenacin	0.1268 (0.0070)	Beta	ODPRN analysis of claims
	Solifenacin	0.0901 (0.0026)	Beta	Mean of all treatments
	Trospium	0.0943 (0.0156)	Beta	
	Fesoterodine	0.0935 (0.0064)	Beta	
	Mirabegron	0.1287 (0.0469)	Beta	
Monthly probability of OAB resolution		0.0030 (0.0025)	Beta	[30]
Probability of adverse events with no therapy	Constipation	0.0238 (0.0188-0.0289)	Beta	Companion network meta-analysis
	Dry mouth	0.0589 (0.0490-0.0688)	Beta	
Odds ratio for probability of constipation versus no therapy	oxybutynin IR	1.282 (0.879-1.866)	Lognormal	Companion network meta-analysis
	oxybutynin ER	1.385 (0.867-2.171)	Lognormal	
	oxybutynin trans	0.166 (0.007-1.633)	Lognormal	
	oxybutynin gel	1.312 (0.348-5.433)	Lognormal	
	tolterodine IR	1.542 (1.141-2.031)	Lognormal	
	tolterodine ER	1.739 (1.382-2.177)	Lognormal	
	darifenacin	3.477 (2.058-6.118)	Lognormal	
	solifenacin	3.968 (3.059-5.224)	Lognormal	
	trospium	2.452 (1.441-4.297)	Lognormal	
	fesoterodine	2.240 (1.780-2.837)	Lognormal	
	mirabegron	1.819 (1.290-2.568)	Lognormal	
Probability of dry mouth	oxybutynin IR	13.380 (9.363-19.590)	Lognormal	Companion network meta-analysis
	oxybutynin ER	5.425 (3.112-9.501)	Lognormal	
	oxybutynin trans	1.184 (0.332-4.229)	Lognormal	
	oxybutynin gel	2.693 (0.834-8.926)	Lognormal	
	tolterodine IR	4.454 (3.267-6.138)	Lognormal	
	tolterodine ER	2.629 (2.011-3.434)	Lognormal	
	darifenacin	5.702 (2.870-11.690)	Lognormal	
	solifenacin	3.962 (2.760-5.715)	Lognormal	
	trospium	3.236 (1.643-6.340)	Lognormal	
	fesoterodine	5.495 (4.129-7.298)	Lognormal	
	mirabegron	0.953 (0.646-1.394)	Lognormal	
Disutility of dry		-0.0357	Fixed	[35]

Input	Description	Value (SE/95% CI)	Distribution	Source
mouth or constipation (per annum)				

Note: Figures in parenthesis are standard errors for data characterized normal distributions, alpha and beta coefficients for data characterized by beta distributions and 95% CI for data characterized by log-normal and gamma distributions.

Appendix B2: Subgroup Analysis by Micturition and Incontinence Level at Baseline

Exhibit 16: Subgroup analysis for Micturition Level 1, Incontinence Level 2

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.712	$0.00	$0.00	$0.00
Solifenacin	0.720	$187.78	$23,336.95	$23,336.95
Mirabegron	0.720	$464.08	$56,625.63	$1,852,496.88
Dominated				
Oxybutynin IR	0.716	$145.36	$32,800.20	Subject to extended dominance through No therapy and Solifenacin
Fesoterodine	0.719	$442.24	$65,439.29	Dominated by Solifenacin
Trospium	0.719	$442.69	$67,116.90	Dominated by Solifenacin, Fesoterodine
Darifenacin	0.718	$476.93	$73,443.86	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin transdermal	0.719	$524.62	$73,924.72	Dominated by Solifenacin, Mirabegron
Tolterodine ER	0.719	$539.81	$81,266.70	Dominated by Solifenacin, Fesoterodine, Mirabegron, Oxybutynin transdermal
Oxybutynin gel	0.719	$553.56	$82,853.35	Dominated by Solifenacin, Fesoterodine, Mirabegron, Oxybutynin transdermal
Tolterodine IR	0.718	$539.74	$83,934.98	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal
Oxybutynin ER	0.719	$645.17	$85,917.67	Dominated by Solifenacin, Mirabegron

Exhibit 17: Subgroup analysis for Micturition Level 1, Incontinence Level 3

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.704	$0.00	$0.00	$0.00
Solifenacin	0.714	$187.78	$19,721.56	$19,721.56
Dominated				
Oxybutynin IR	0.710	$145.36	$26,994.94	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.714	$464.08	$49,160.18	Dominated by Solifenacin

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Fesoterodine	0.712	$442.24	$56,540.77	Dominated by Solifenacin
Trospium	0.712	$442.69	$58,106.51	Dominated by Solifenacin, Fesoterodine
Darifenacin	0.712	$476.93	$63,984.52	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin transdermal	0.712	$524.62	$64,198.42	Dominated by Solifenacin, Mirabegron
Tolterodine ER	0.712	$539.81	$70,924.20	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal
Oxybutynin ER	0.713	$645.17	$71,330.00	Dominated by Solifenacin, Mirabegron
Oxybutynin gel	0.712	$553.56	$72,434.11	Dominated by Solifenacin, Fesoterodine, Mirabegron, Oxybutynin transdermal
Tolterodine IR	0.712	$539.74	$73,049.46	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal

Exhibit 18: Subgroup analysis for Micturition Level 1, Incontinence Level 4

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.696	$0.00	$0.00	$0.00
Solifenacin	0.705	$187.78	$19,388.75	$19,388.75
Dominated				
Oxybutynin IR	0.701	$145.36	$26,686.87	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.705	$464.08	$49,677.97	Dominated by Solifenacin
Fesoterodine	0.703	$442.24	$57,701.11	Dominated by Solifenacin
Trospium	0.703	$442.69	$58,847.93	Dominated by Solifenacin, Fesoterodine
Oxybutynin transdermal	0.704	$524.62	$64,954.94	Dominated by Solifenacin, Mirabegron
Darifenacin	0.703	$476.93	$66,449.76	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin ER	0.705	$645.17	$68,470.51	Dominated by Solifenacin
Tolterodine ER	0.703	$539.81	$72,821.27	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal
Oxybutynin gel	0.703	$553.56	$74,435.73	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal
Tolterodine IR	0.703	$539.74	$75,167.57	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal

Exhibit 19: Subgroup analysis for Micturition Level 1, Incontinence Level 5

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.687	$0.00	$0.00	$0.00
Solifenacin	0.693	$187.78	$32,790.49	$32,790.49
Oxybutynin ER	0.694	$645.17	$103,024.73	$853,920.26
Dominated				
Oxybutynin IR	0.690	$145.36	$52,757.04	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.692	$464.08	$94,566.80	Dominated by Solifenacin
Trospium	0.691	$442.69	$115,518.88	Dominated by Solifenacin
Oxybutynin transdermal	0.692	$524.62	$124,371.86	Dominated by Solifenacin, Mirabegron
Fesoterodine	0.691	$442.24	$124,814.52	Dominated by Solifenacin
Tolterodine ER	0.691	$539.81	$158,580.05	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal
Oxybutynin gel	0.691	$553.56	$161,977.38	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal
Darifenacin	0.690	$476.93	$169,361.64	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Tolterodine IR	0.691	$539.74	$170,949.51	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal

Exhibit 20: Subgroup analysis for Micturition Level 2, Incontinence Level 1

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.709	$0.00	$0.00	$0.00
Solifenacin	0.718	$187.78	$21,825.15	$21,825.15
Dominated				
Oxybutynin IR	0.714	$145.36	$31,213.02	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.718	$464.08	$54,512.81	Dominated by Solifenacin
Trospium	0.717	$442.69	$59,321.30	Dominated by Solifenacin
Fesoterodine	0.717	$442.24	$60,354.92	Dominated by Solifenacin
Darifenacin	0.716	$476.93	$67,932.83	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin transdermal	0.717	$524.62	$73,278.03	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Tolterodine ER	0.716	$539.81	$77,443.88	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Oxybutynin gel	0.717	$553.56	$77,644.63	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal
Tolterodine IR	0.716	$539.74	$78,657.98	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal
Oxybutynin ER	0.717	$645.17	$79,748.04	Dominated by Solifenacin, Mirabegron

Exhibit 21: Subgroup analysis for Micturition Level 2, Incontinence Level 2

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.703	$0.00	$0.00	$0.00
Solifenacin	0.714	$187.78	$17,879.59	$17,879.59
Dominated				
Oxybutynin IR	0.709	$145.36	$24,587.07	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.714	$464.08	$45,359.77	Dominated by Solifenacin
Trospium	0.712	$442.69	$49,828.57	Dominated by Solifenacin
Fesoterodine	0.712	$442.24	$50,073.57	Dominated by Solifenacin
Darifenacin	0.712	$476.93	$56,497.25	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin transdermal	0.712	$524.62	$60,647.00	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Tolterodine ER	0.712	$539.81	$64,515.82	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal
Oxybutynin ER	0.713	$645.17	$64,751.68	Dominated by Solifenacin, Mirabegron
Oxybutynin gel	0.712	$553.56	$64,976.77	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal
Tolterodine IR	0.712	$539.74	$65,428.73	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal

Exhibit 22: Subgroup analysis for Micturition Level 2, Incontinence Level 3

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.696	$0.00	$0.00	$0.00
Solifenacin	0.708	$187.78	$15,677.64	$15,677.64
Dominated				
Oxybutynin IR	0.703	$145.36	$21,173.81	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.707	$464.08	$40,440.33	Dominated by Solifenacin

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Trospium	0.706	$442.69	$44,684.34	Dominated by Solifenacin
Fesoterodine	0.706	$442.24	$44,691.48	Dominated by Solifenacin
Darifenacin	0.705	$476.93	$50,728.17	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin transdermal	0.706	$524.62	$53,942.40	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin ER	0.707	$645.17	$56,104.41	Dominated by Solifenacin
Tolterodine ER	0.705	$539.81	$57,821.94	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal
Oxybutynin gel	0.705	$553.56	$58,389.90	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal
Tolterodine IR	0.705	$539.74	$58,619.47	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal

Exhibit 23: Subgroup analysis for Micturition Level 2, Incontinence Level 4

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.687	$0.00	$0.00	$0.00
Solifenacin	0.699	$187.78	$15,466.59	$15,466.59
Dominated				
Oxybutynin IR	0.694	$145.36	$20,983.82	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.699	$464.08	$40,790.08	Dominated by Solifenacin
Trospium	0.697	$442.69	$45,121.51	Dominated by Solifenacin
Fesoterodine	0.697	$442.24	$45,413.33	Dominated by Solifenacin
Darifenacin	0.696	$476.93	$52,265.45	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin ER	0.699	$645.17	$54,320.10	Dominated by Solifenacin
Oxybutynin transdermal	0.697	$524.62	$54,475.50	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Tolterodine ER	0.696	$539.81	$59,076.64	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal
Oxybutynin gel	0.697	$553.56	$59,683.65	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal
Tolterodine IR	0.696	$539.74	$59,975.65	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal

Exhibit 24: Subgroup analysis for Micturition Level 2, Incontinence Level 5

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.679	$0.00	$0.00	$0.00
Solifenacin	0.687	$187.78	$22,948.49	$22,948.49
Oxybutynin ER	0.688	$645.17	$74,013.92	$856,181.82
Dominated				
Oxybutynin IR	0.683	$145.36	$34,318.29	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.686	$464.08	$66,841.99	Dominated by Solifenacin
Trospium	0.685	$442.69	$72,327.37	Dominated by Solifenacin
Fesoterodine	0.685	$442.24	$78,732.94	Dominated by Solifenacin
Oxybutynin transdermal	0.685	$524.62	$90,892.64	Dominated by Solifenacin, Trospium, Mirabegron
Darifenacin	0.684	$476.93	$100,113.53	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Tolterodine ER	0.684	$539.81	$105,253.45	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal
Oxybutynin gel	0.684	$553.56	$105,326.35	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal
Tolterodine IR	0.684	$539.74	$108,465.72	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal

Exhibit 25: Subgroup analysis for Micturition Level 3, Incontinence Level 1

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.696	$0.00	$0.00	$0.00
Solifenacin	0.706	$187.78	$18,829.89	$18,829.89
Dominated				
Oxybutynin IR	0.701	$145.36	$27,226.63	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.705	$464.08	$49,674.55	Dominated by Solifenacin
Trospium	0.705	$442.69	$49,963.15	Dominated by Solifenacin
Fesoterodine	0.704	$442.24	$53,058.42	Dominated by Solifenacin
Darifenacin	0.704	$476.93	$60,693.62	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin ER	0.705	$645.17	$66,905.11	Dominated by Solifenacin
Oxybutynin transdermal	0.703	$524.62	$68,749.93	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin
Oxybutynin gel	0.704	$553.56	$69,931.08	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Tolterodine ER	0.703	$539.81	$70,763.79	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal
Tolterodine IR	0.703	$539.74	$70,775.19	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal

Exhibit 26: Subgroup analysis for Micturition Level 3, Incontinence Level 2

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.690	$0.00	$0.00	$0.00
Solifenacin	0.702	$187.78	$15,818.27	$15,818.27
Dominated				
Oxybutynin IR	0.696	$145.36	$22,044.59	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.701	$464.08	$41,959.18	Dominated by Solifenacin
Trospium	0.700	$442.69	$43,054.82	Dominated by Solifenacin
Fesoterodine	0.700	$442.24	$44,945.62	Dominated by Solifenacin
Darifenacin	0.699	$476.93	$51,398.68	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin ER	0.701	$645.17	$56,020.32	Dominated by Solifenacin
Oxybutynin transdermal	0.699	$524.62	$57,512.00	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin
Oxybutynin gel	0.699	$553.56	$59,485.86	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Tolterodine ER	0.699	$539.81	$59,812.12	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal
Tolterodine IR	0.699	$539.74	$59,881.02	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal

Exhibit 27: Subgroup analysis for Micturition Level 3, Incontinence Level 3

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.682	$0.00	$0.00	$0.00
Solifenacin	0.696	$187.78	$14,069.95	$14,069.95
Dominated				
Oxybutynin IR	0.690	$145.36	$19,260.78	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.695	$464.08	$37,715.20	Dominated by Solifenacin
Trospium	0.694	$442.69	$39,159.48	Dominated by Solifenacin
Fesoterodine	0.693	$442.24	$40,561.17	Dominated by Solifenacin
Darifenacin	0.692	$476.93	$46,579.46	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin ER	0.695	$645.17	$49,429.19	Dominated by Solifenacin
Oxybutynin transdermal	0.692	$524.62	$51,447.98	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin
Oxybutynin gel	0.693	$553.56	$53,917.51	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Tolterodine ER	0.692	$539.81	$54,014.88	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Tolterodine IR	0.692	$539.74	$54,126.75	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal

Exhibit 28: Subgroup analysis for Micturition Level 3, Incontinence Level 4

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.674	$0.00	$0.00	$0.00
Solifenacin	0.687	$187.78	$13,899.73	$13,899.73
Dominated				
Oxybutynin IR	0.681	$145.36	$19,103.44	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.686	$464.08	$38,019.22	Dominated by Solifenacin
Trospium	0.685	$442.69	$39,494.82	Dominated by Solifenacin
Fesoterodine	0.684	$442.24	$41,154.87	Dominated by Solifenacin
Darifenacin	0.684	$476.93	$47,872.38	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin ER	0.687	$645.17	$48,038.95	Dominated by Solifenacin
Oxybutynin transdermal	0.684	$524.62	$51,932.71	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin gel	0.684	$553.56	$55,018.79	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal
Tolterodine ER	0.684	$539.81	$55,108.24	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal
Tolterodine IR	0.683	$539.74	$55,280.97	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal

Exhibit 29: Subgroup analysis for Micturition Level 3, Incontinence Level 5

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.665	$0.00	$0.00	$0.00
Solifenacin	0.675	$187.78	$19,660.20	$19,660.20
Oxybutynin ER	0.676	$645.17	$62,821.88	$636,523.60
Dominated				
Oxybutynin IR	0.670	$145.36	$29,559.73	Subject to extended dominance through No therapy and Solifenacin
Trospium	0.673	$442.69	$58,880.95	Dominated by Solifenacin
Mirabegron	0.673	$464.08	$59,710.85	Dominated by Solifenacin
Fesoterodine	0.672	$442.24	$66,757.20	Dominated by Solifenacin

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Oxybutynin transdermal	0.672	$524.62	$84,027.93	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Darifenacin	0.671	$476.93	$85,146.72	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin gel	0.671	$553.56	$91,617.86	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal
Tolterodine ER	0.671	$539.81	$93,285.15	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal
Tolterodine IR	0.671	$539.74	$94,024.91	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal

Exhibit 30: Subgroup analysis for Micturition Level 4, Incontinence Level 1

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.681	$0.00	$0.00	$0.00
Solifenacin	0.691	$187.78	$19,655.44	$19,655.44
Dominated				
Oxybutynin IR	0.686	$145.36	$29,142.75	Subject to extended dominance through No therapy and Solifenacin
Trospium	0.690	$442.69	$51,772.06	Dominated by Solifenacin
Mirabegron	0.690	$464.08	$52,694.34	Dominated by Solifenacin
Fesoterodine	0.689	$442.24	$56,093.85	Dominated by Solifenacin
Darifenacin	0.689	$476.93	$64,718.76	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin ER	0.691	$645.17	$68,979.98	Dominated by Solifenacin
Oxybutynin transdermal	0.689	$524.62	$73,556.34	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin
Oxybutynin gel	0.689	$553.56	$74,292.54	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Tolterodine IR	0.689	$539.74	$75,400.96	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin
Tolterodine ER	0.689	$539.81	$75,529.91	Dominated by Tolterodine IR, Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin

Exhibit 31: Subgroup analysis for Micturition Level 4, Incontinence Level 2

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.675	$0.00	$0.00	$0.00
Solifenacin	0.687	$187.78	$16,396.80	$16,396.80
Dominated				

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Oxybutynin IR	0.682	$145.36	$23,284.12	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.686	$464.08	$44,093.61	Dominated by Solifenacin
Trospium	0.685	$442.69	$44,391.39	Dominated by Solifenacin
Fesoterodine	0.685	$442.24	$47,104.87	Dominated by Solifenacin
Darifenacin	0.684	$476.93	$54,256.34	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin ER	0.687	$645.17	$57,467.69	Dominated by Solifenacin
Oxybutynin transdermal	0.684	$524.62	$60,837.51	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin
Oxybutynin gel	0.684	$553.56	$62,612.60	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Tolterodine IR	0.684	$539.74	$63,159.35	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal
Tolterodine ER	0.684	$539.81	$63,182.02	Dominated by Tolterodine IR, Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal

Exhibit 32: Subgroup analysis for Micturition Level 4, Incontinence Level 3

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.668	$0.00	$0.00	$0.00
Solifenacin	0.681	$187.78	$14,525.82	$14,525.82
Dominated				
Oxybutynin IR	0.675	$145.36	$20,200.35	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.680	$464.08	$39,430.86	Dominated by Solifenacin
Trospium	0.679	$442.69	$40,262.04	Dominated by Solifenacin
Fesoterodine	0.678	$442.24	$42,311.50	Dominated by Solifenacin
Darifenacin	0.678	$476.93	$48,914.19	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin ER	0.681	$645.17	$50,552.59	Dominated by Solifenacin
Oxybutynin transdermal	0.678	$524.62	$54,093.06	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin
Oxybutynin gel	0.678	$553.56	$56,473.69	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Tolterodine ER	0.677	$539.81	$56,748.26	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal
Tolterodine IR	0.677	$539.74	$56,791.27	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal

Exhibit 33: Subgroup analysis for Micturition Level 4, Incontinence Level 4

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.659	$0.00	$0.00	$0.00
Solifenacin	0.672	$187.78	$14,344.47	$14,344.47
Oxybutynin ER	0.672	$645.17	$49,099.37	$9,267,258.23
Dominated				
Oxybutynin IR	0.667	$145.36	$20,027.35	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.671	$464.08	$39,763.29	Dominated by Solifenacin
Trospium	0.670	$442.69	$40,616.62	Dominated by Solifenacin
Fesoterodine	0.670	$442.24	$42,957.95	Dominated by Solifenacin
Darifenacin	0.669	$476.93	$50,341.96	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin transdermal	0.669	$524.62	$54,629.16	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin gel	0.669	$553.56	$57,683.04	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal
Tolterodine ER	0.669	$539.81	$57,956.31	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal
Tolterodine IR	0.669	$539.74	$58,063.26	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal

Exhibit 34: Subgroup analysis for Micturition Level 4, Incontinence Level 5

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.651	$0.00	$0.00	$0.00
Solifenacin	0.660	$187.78	$20,561.90	$20,561.90
Oxybutynin ER	0.661	$645.17	$64,647.76	$539,776.37
Dominated				
Oxybutynin IR	0.656	$145.36	$31,832.01	Subject to extended dominance through No therapy and Solifenacin
Trospium	0.658	$442.69	$61,409.56	Dominated by Solifenacin
Mirabegron	0.658	$464.08	$64,128.41	Dominated by Solifenacin
Fesoterodine	0.657	$442.24	$71,634.39	Dominated by Solifenacin
Oxybutynin transdermal	0.657	$524.62	$91,321.22	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Darifenacin	0.656	$476.93	$93,286.12	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin gel	0.657	$553.56	$99,251.54	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal
Tolterodine ER	0.656	$539.81	$101,749.19	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal
Tolterodine IR	0.656	$539.74	$102,368.13	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal

Exhibit 35: Subgroup analysis for Micturition Level 5, Incontinence Level 1

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.670	$0.00	$0.00	$0.00
Solifenacin	0.677	$187.78	$26,468.56	$26,468.56
Dominated				
Oxybutynin IR	0.674	$145.36	$42,831.92	Subject to extended dominance through No therapy and Solifenacin
Trospium	0.677	$442.69	$69,417.71	Dominated by Solifenacin
Mirabegron	0.677	$464.08	$71,645.62	Dominated by Solifenacin
Fesoterodine	0.676	$442.24	$77,902.91	Dominated by Solifenacin
Oxybutynin ER	0.677	$645.17	$91,366.69	Dominated by Solifenacin
Darifenacin	0.675	$476.93	$91,911.71	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin transdermal	0.675	$524.62	$101,078.67	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin gel	0.676	$553.56	$102,637.81	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Tolterodine ER	0.675	$539.81	$105,124.77	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal
Tolterodine IR	0.675	$539.74	$105,660.57	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal

Exhibit 36: Subgroup analysis for Micturition Level 5, Incontinence Level 2

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.664	$0.00	$0.00	$0.00
Solifenacin	0.673	$187.78	$20,880.46	$20,880.46
Dominated				
Oxybutynin IR	0.669	$145.36	$31,268.62	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.672	$464.08	$56,627.58	Dominated by Solifenacin
Trospium	0.672	$442.69	$56,763.35	Dominated by Solifenacin
Fesoterodine	0.671	$442.24	$61,582.24	Dominated by Solifenacin
Darifenacin	0.671	$476.93	$72,152.35	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin ER	0.673	$645.17	$72,207.22	Dominated by Solifenacin
Oxybutynin transdermal	0.671	$524.62	$78,520.73	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Oxybutynin gel	0.671	$553.56	$81,606.51	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Tolterodine ER	0.671	$539.81	$82,644.60	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal
Tolterodine IR	0.671	$539.74	$83,092.32	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal

Exhibit 37: Subgroup analysis for Micturition Level 5, Incontinence Level 3

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.657	$0.00	$0.00	$0.00
Solifenacin	0.667	$187.78	$17,938.16	$17,938.16
Oxybutynin ER	0.667	$645.17	$61,616.85	$181,984,435.82
Dominated				
Oxybutynin IR	0.662	$145.36	$25,948.88	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.666	$464.08	$49,161.64	Dominated by Solifenacin
Trospium	0.665	$442.69	$50,182.16	Dominated by Solifenacin
Fesoterodine	0.665	$442.24	$53,638.11	Dominated by Solifenacin
Darifenacin	0.664	$476.93	$63,002.05	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin transdermal	0.664	$524.62	$67,636.47	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin gel	0.664	$553.56	$71,479.33	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal
Tolterodine ER	0.664	$539.81	$71,971.43	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal
Tolterodine IR	0.664	$539.74	$72,410.37	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal

Exhibit 38: Subgroup analysis for Micturition Level 5, Incontinence Level 4

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.648	$0.00	$0.00	$0.00
Solifenacin	0.659	$187.78	$17,662.39	$17,662.39
Oxybutynin ER	0.659	$645.17	$59,471.39	$2,109,672.51
Dominated				
Oxybutynin IR	0.654	$145.36	$25,664.10	Subject to extended dominance through No therapy and Solifenacin

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Mirabegron	0.657	$464.08	$49,679.47	Dominated by Solifenacin
Trospium	0.657	$442.69	$50,734.19	Dominated by Solifenacin
Fesoterodine	0.656	$442.24	$54,681.26	Dominated by Solifenacin
Darifenacin	0.655	$476.93	$65,390.75	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin transdermal	0.656	$524.62	$68,476.72	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin gel	0.656	$553.56	$73,427.83	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal
Tolterodine ER	0.655	$539.81	$73,925.71	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal
Tolterodine IR	0.655	$539.74	$74,491.05	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal

Exhibit 39: Subgroup analysis for Micturition Level 5, Incontinence Level 5

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.640	$0.00	$0.00	$0.00
Solifenacin	0.647	$187.78	$28,139.04	$28,139.04
Oxybutynin ER	0.648	$645.17	$83,918.05	$450,710.42
Dominated				
Oxybutynin IR	0.643	$145.36	$48,904.20	Subject to extended dominance through No therapy and Solifenacin
Trospium	0.645	$442.69	$87,918.13	Dominated by Solifenacin
Mirabegron	0.645	$464.08	$94,572.24	Dominated by Solifenacin, Trospium
Fesoterodine	0.644	$442.24	$111,495.17	Dominated by Solifenacin
Oxybutynin transdermal	0.644	$524.62	$137,957.30	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin gel	0.643	$553.56	$157,279.49	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal
Darifenacin	0.643	$476.93	$162,648.07	Dominated by Oxybutynin IR, Solifenacin, Fesoterodine, Trospium, Mirabegron
Tolterodine ER	0.643	$539.81	$163,912.79	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal
Tolterodine IR	0.643	$539.74	$167,490.09	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal

Appendix B3: Deterministic Sensitivity Analysis

Exhibit 40: Timing of Discontinuation of Therapy: Patients discontinue therapy mid-cycle rather than at the end of the cycle

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.684	$0.00	$0.00	$0.00
Solifenacin	0.693	$187.78	$19,869.53	$19,869.53
Dominated				
Oxybutynin IR	0.689	$145.36	$30,139.65	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.692	$464.08	$53,199.78	Dominated by Solifenacin
Trospium	0.692	$442.69	$56,248.19	Dominated by Solifenacin
Fesoterodine	0.691	$442.24	$59,040.37	Dominated by Solifenacin
Darifenacin	0.691	$476.93	$68,767.46	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin ER	0.693	$645.17	$69,851.46	Dominated by Solifenacin
Oxybutynin transdermal	0.691	$524.62	$73,578.50	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin gel	0.691	$553.56	$78,081.86	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal
Tolterodine ER	0.691	$539.81	$78,457.14	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal
Tolterodine IR	0.691	$539.74	$79,285.41	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal

Exhibit 41: The distribution of symptoms in those who discontinue therapy after 3 months does not differ from the distribution in those who remain on therapy.

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.684	$0.00	$0.00	$0.00
Solifenacin	0.690	$187.78	$30,094.50	$30,094.50
Oxybutynin ER	0.691	$645.17	$93,412.71	$685,743.17
Dominated				
Oxybutynin IR	0.686	$145.36	$53,112.99	Subject to extended dominance through No therapy and Solifenacin
Trospium	0.689	$442.69	$88,081.10	Dominated by Solifenacin
Mirabegron	0.688	$464.08	$96,735.37	Dominated by Solifenacin, Trospium
Fesoterodine	0.688	$442.24	$110,455.71	Dominated by Solifenacin
Oxybutynin transdermal	0.687	$524.62	$143,366.24	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Oxybutynin gel	0.687	$553.56	$153,578.15	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal
Darifenacin	0.687	$476.93	$154,162.55	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Tolterodine ER	0.687	$539.81	$161,529.84	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal
Tolterodine IR	0.687	$539.74	$163,224.49	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal

Exhibit 42: Patients whose symptoms worsen by one or more levels are assumed to discontinue therapy after 3 months.

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.684	$0.00	$0.00	$0.00
Solifenacin	0.698	$187.78	$13,353.65	$13,353.65
Dominated				
Oxybutynin IR	0.692	$145.36	$17,760.55	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.697	$464.08	$33,769.07	Dominated by Solifenacin
Fesoterodine	0.696	$442.24	$36,748.40	Dominated by Solifenacin
Trospium	0.696	$442.69	$37,206.16	Dominated by Solifenacin, Fesoterodine
Darifenacin	0.695	$476.93	$40,887.22	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin transdermal	0.695	$524.62	$44,988.41	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin
Tolterodine ER	0.695	$539.81	$47,417.28	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal
Tolterodine IR	0.695	$539.74	$47,860.52	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal
Oxybutynin gel	0.695	$553.56	$47,926.15	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal
Oxybutynin ER	0.697	$645.17	$48,801.92	Dominated by Solifenacin, Mirabegron

Exhibit 43: The frequency and severity of adverse events in those discontinuing therapy does not differ from those remaining on therapy after 3 months

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.683	$0.00	$0.00	$0.00
Solifenacin	0.692	$187.78	$21,205.09	$21,205.09
Mirabegron	0.692	$464.08	$51,065.20	$1,187,830.68

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Dominated				
Oxybutynin IR	0.687	$145.36	$35,433.22	Subject to extended dominance through No therapy and Solifenacin
Trospium	0.691	$442.69	$56,544.04	Dominated by Solifenacin
Fesoterodine	0.690	$442.24	$64,589.66	Dominated by Solifenacin
Oxybutynin transdermal	0.691	$524.62	$68,557.51	Dominated by Solifenacin, Trospium, Mirabegron
Oxybutynin ER	0.692	$645.17	$72,364.67	Dominated by Mirabegron
Oxybutynin gel	0.690	$553.56	$77,217.47	Dominated by Solifenacin, Trospium, Mirabegron, Oxybutynin transdermal
Tolterodine ER	0.690	$539.81	$77,998.90	Dominated by Solifenacin, Trospium, Mirabegron, Oxybutynin transdermal
Darifenacin	0.689	$476.93	$78,262.65	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Tolterodine IR	0.689	$539.74	$82,950.19	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal

Exhibit 44: Additional physician visits in excess of those associated with supportive care (no therapy), occur only at treatment switches

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.684	$0.00	$0.00	$0.00
Solifenacin	0.693	$150.86	$15,303.78	$15,303.78
Dominated				
Oxybutynin IR	0.689	$108.55	$20,493.88	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.693	$426.43	$47,043.49	Dominated by Solifenacin
Trospium	0.692	$406.41	$48,813.25	Dominated by Solifenacin
Fesoterodine	0.691	$405.58	$51,511.73	Dominated by Solifenacin
Darifenacin	0.691	$439.58	$60,330.35	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin ER	0.693	$607.89	$62,344.06	Dominated by Solifenacin
Oxybutynin transdermal	0.691	$487.34	$65,071.60	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin gel	0.691	$516.28	$69,180.67	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal
Tolterodine ER	0.691	$502.52	$69,383.54	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal
Tolterodine IR	0.691	$502.45	$69,995.71	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal

Exhibit 45: The discontinuation rate with oxybutynin ER is equated to that of solifenacin, the lowest discontinuation rate

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.684	$0.00	$0.00	$0.00
Solifenacin	0.693	$187.78	$19,049.70	$19,049.70
Oxybutynin ER	0.695	$714.70	$64,242.12	$415,668.04
Dominated				
Oxybutynin IR	0.689	$145.36	$27,442.19	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.693	$464.08	$51,197.47	Dominated by Solifenacin
Trospium	0.692	$442.69	$53,170.58	Dominated by Solifenacin
Fesoterodine	0.691	$442.24	$56,168.19	Dominated by Solifenacin
Darifenacin	0.691	$476.93	$65,456.58	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin transdermal	0.691	$524.62	$70,050.41	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin gel	0.691	$553.56	$74,177.15	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal
Tolterodine ER	0.691	$539.81	$74,531.85	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal
Tolterodine IR	0.691	$539.74	$75,190.16	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal

Exhibit 46: The discontinuation rate with oxybutynin ER is equated to that of trospium, the highest discontinuation rate

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.684	$0.00	$0.00	$0.00
Solifenacin	0.693	$187.78	$19,049.70	$19,049.70
Dominated				
Oxybutynin IR	0.689	$145.36	$27,442.19	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.693	$464.08	$51,197.47	Dominated by Solifenacin
Trospium	0.692	$442.69	$53,170.58	Dominated by Solifenacin
Fesoterodine	0.691	$442.24	$56,168.19	Dominated by Solifenacin
Darifenacin	0.691	$476.93	$65,456.58	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin ER	0.693	$636.85	$66,427.67	Dominated by Solifenacin
Oxybutynin transdermal	0.691	$524.62	$70,050.41	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin gel	0.691	$553.56	$74,177.15	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal
Tolterodine ER	0.691	$539.81	$74,531.85	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal
Tolterodine IR	0.691	$539.74	$75,190.16	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal

Exhibit 47: The discontinuation rate with oxybutynin transdermal is equated to that of solifenacin, the lowest discontinuation rate

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.684	$0.00	$0.00	$0.00
Solifenacin	0.693	$187.78	$19,049.70	$19,049.70
Dominated				
Oxybutinin IR	0.689	$145.36	$27,442.19	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.693	$464.08	$51,197.47	Dominated by Solifenacin
Trospium	0.692	$442.69	$53,170.58	Dominated by Solifenacin
Fesoterodine	0.691	$442.24	$56,168.19	Dominated by Solifenacin
Darifenacin	0.691	$476.93	$65,456.58	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutinin ER	0.693	$645.17	$66,168.22	Dominated by Solifenacin
Oxybutinin transdermal	0.692	$578.35	$67,511.69	Dominated by Solifenacin, Mirabegron
Oxybutinin gel	0.691	$553.56	$74,177.15	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Tolterodine ER	0.691	$539.81	$74,531.85	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin
Tolterodine IR	0.691	$539.74	$75,190.16	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin

Exhibit 48: The discontinuation rate with oxybutynin transdermal is equated to that of trospium, the highest discontinuation rate

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.684	$0.00	$0.00	$0.00
Solifenacin	0.693	$187.78	$19,049.70	$19,049.70
Dominated				
Oxybutinin IR	0.689	$145.36	$27,442.19	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.693	$464.08	$51,197.47	Dominated by Solifenacin
Trospium	0.692	$442.69	$53,170.58	Dominated by Solifenacin
Fesoterodine	0.691	$442.24	$56,168.19	Dominated by Solifenacin
Darifenacin	0.691	$476.93	$65,456.58	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutinin ER	0.693	$645.17	$66,168.22	Dominated by Solifenacin
Oxybutinin transdermal	0.691	$518.19	$70,393.21	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutinin gel	0.691	$553.56	$74,177.15	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Tolterodine ER	0.691	$539.81	$74,531.85	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutinin transdermal

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Tolterodine IR	0.691	$539.74	$75,190.16	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutinin transdermal

Exhibit 49: The discontinuation rate with oxybutynin gel is equated to that of solifenacin, the lowest discontinuation rate

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.684	$0.00	$0.00	$0.00
Solifenacin	0.693	$187.78	$19,049.70	$19,049.70
Dominated				
Oxybutinin IR	0.689	$145.36	$27,442.19	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.693	$464.08	$51,197.47	Dominated by Solifenacin
Trospium	0.692	$442.69	$53,170.58	Dominated by Solifenacin
Fesoterodine	0.691	$442.24	$56,168.19	Dominated by Solifenacin
Darifenacin	0.691	$476.93	$65,456.58	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutinin ER	0.693	$645.17	$66,168.22	Dominated by Solifenacin
Oxybutinin transdermal	0.691	$524.62	$70,050.41	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutinin gel	0.692	$611.08	$71,315.50	Dominated by Solifenacin, Mirabegron
Tolterodine ER	0.691	$539.81	$74,531.85	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutinin transdermal
Tolterodine IR	0.691	$539.74	$75,190.16	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutinin transdermal

Exhibit 50: The discontinuation rate with oxybutynin gel is equated to that of trospium, the highest discontinuation rate

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.684	$0.00	$0.00	$0.00
Solifenacin	0.693	$187.78	$19,049.70	$19,049.70
Dominated				
Oxybutinin IR	0.689	$145.36	$27,442.19	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.693	$464.08	$51,197.47	Dominated by Solifenacin
Trospium	0.692	$442.69	$53,170.58	Dominated by Solifenacin
Fesoterodine	0.691	$442.24	$56,168.19	Dominated by Solifenacin
Darifenacin	0.691	$476.93	$65,456.58	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutinin ER	0.693	$645.17	$66,168.22	Dominated by Solifenacin

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Oxybutinin transdermal	0.691	$524.62	$70,050.41	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Tolterodine ER	0.691	$539.81	$74,531.85	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutinin transdermal
Oxybutinin gel	0.691	$546.68	$74,565.22	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutinin transdermal
Tolterodine IR	0.691	$539.74	$75,190.16	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutinin transdermal

Exhibit 51: The discontinuation rate with tolterodine ER is equated to that of solifenacin, the lowest discontinuation rate

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.684	$0.00	$0.00	$0.00
Solifenacin	0.694	$189.28	$19,145.42	$19,145.42
Dominated				
Oxybutinin IR	0.689	$150.52	$27,885.07	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.693	$466.23	$51,198.34	Dominated by Solifenacin
Trospium	0.692	$444.70	$53,161.81	Dominated by Solifenacin
Fesoterodine	0.692	$444.01	$56,147.12	Dominated by Solifenacin
Darifenacin	0.691	$479.35	$65,366.11	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutinin ER	0.693	$647.99	$66,085.08	Dominated by Solifenacin
Oxybutinin transdermal	0.691	$527.44	$69,914.10	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Tolterodine ER	0.692	$597.78	$71,433.37	Dominated by Solifenacin, Mirabegron
Oxybutinin gel	0.691	$556.38	$74,010.24	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutinin transdermal
Tolterodine IR	0.691	$542.56	$75,009.00	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutinin transdermal

Exhibit 52: The discontinuation rate with tolterodine ER is equated to that of trospium, the highest discontinuation rate

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.684	$0.00	$0.00	$0.00
Solifenacin	0.693	$187.60	$19,037.86	$19,037.86
Dominated				
Oxybutinin IR	0.689	$144.73	$27,386.49	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.693	$463.82	$51,197.24	Dominated by Solifenacin

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Trospium	0.692	$442.44	$53,171.52	Dominated by Solifenacin
Fesoterodine	0.691	$442.02	$56,170.66	Dominated by Solifenacin
Darifenacin	0.691	$476.63	$65,467.54	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutinin ER	0.693	$644.83	$66,178.29	Dominated by Solifenacin
Oxybutinin transdermal	0.691	$524.28	$70,067.01	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutinin gel	0.691	$553.22	$74,197.52	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutinin transdermal
Tolterodine ER	0.691	$532.78	$74,960.82	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutinin transdermal
Tolterodine IR	0.691	$539.39	$75,212.29	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutinin transdermal

Exhibit 53: The discontinuation rate with mirabegron is equated to that of trospium, the highest discontinuation rate

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.684	$0.00	$0.00	$0.00
Solifenacin	0.693	$187.78	$19,049.70	$19,049.70
Dominated				
Oxybutinin IR	0.689	$145.36	$27,442.19	Subject to extended dominance through No therapy and Solifenacin
Trospium	0.692	$442.69	$53,170.58	Dominated by Solifenacin
Mirabegron	0.691	$418.21	$53,690.78	Dominated by Solifenacin
Fesoterodine	0.691	$442.24	$56,168.19	Dominated by Solifenacin
Darifenacin	0.691	$476.93	$65,456.58	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutinin ER	0.693	$645.17	$66,168.22	Dominated by Solifenacin
Oxybutinin transdermal	0.691	$524.62	$70,050.41	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutinin gel	0.691	$553.56	$74,177.15	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutinin transdermal
Tolterodine ER	0.691	$539.81	$74,531.85	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutinin transdermal
Tolterodine IR	0.691	$539.74	$75,190.16	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutinin transdermal

Exhibit 54: The discontinuation rate with mirabegron is equated to half that of solifenacin, the lowest discontinuation rate

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.684	$0.00	$0.00	$0.00
Solifenacin	0.693	$187.78	$19,049.70	$19,049.70

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Mirabegron	0.695	$544.15	$47,985.65	$240,390.45
Dominated				
Oxybutinin IR	0.689	$145.36	$27,442.19	Subject to extended dominance through No therapy and Solifenacin
Trospium	0.692	$442.69	$53,170.58	Dominated by Solifenacin
Fesoterodine	0.691	$442.24	$56,168.19	Dominated by Solifenacin
Darifenacin	0.691	$476.93	$65,456.58	Dominated by Solifenacin, Fesoterodine, Trospium
Oxybutinin ER	0.693	$645.17	$66,168.22	Dominated by Solifenacin, Mirabegron
Oxybutinin transdermal	0.691	$524.62	$70,050.41	Dominated by Solifenacin, Fesoterodine, Trospium
Oxybutinin gel	0.691	$553.56	$74,177.15	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutinin transdermal
Tolterodine ER	0.691	$539.81	$74,531.85	Dominated by Solifenacin, Fesoterodine, Trospium, Darifenacin, Oxybutinin transdermal
Tolterodine IR	0.691	$539.74	$75,190.16	Dominated by Solifenacin, Fesoterodine, Trospium, Darifenacin, Oxybutinin transdermal

Exhibit 55: Assuming the frequency of adverse events with mirabegron is equal to the frequency with tolterodine ER

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.684	$0.00	$0.00	$0.00
Solifenacin	0.693	$187.78	$19,049.70	$19,049.70
Dominated				
Oxybutynin IR	0.689	$145.36	$27,442.19	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.692	$464.08	$52,617.21	Dominated by Solifenacin
Trospium	0.692	$442.69	$53,170.58	Dominated by Solifenacin
Fesoterodine	0.691	$442.24	$56,168.19	Dominated by Solifenacin
Darifenacin	0.691	$476.93	$65,456.58	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin ER	0.693	$645.17	$66,168.22	Dominated by Solifenacin
Oxybutynin transdermal	0.691	$524.62	$70,050.41	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin gel	0.691	$553.56	$74,177.15	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal
Tolterodine ER	0.691	$539.81	$74,531.85	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal
Tolterodine IR	0.691	$539.74	$75,190.16	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal

Exhibit 56: Assuming OAB symptoms do not resolve in any patients over the course of a year

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.683	$0.00	$0.00	$0.00
Solifenacin	0.693	$188.57	$19,117.30	$19,117.30
Dominated				
Oxybutinin IR	0.688	$146.51	$27,592.22	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.692	$465.22	$51,257.13	Dominated by Solifenacin
Trospium	0.691	$443.44	$53,219.50	Dominated by Solifenacin
Fesoterodine	0.691	$443.02	$56,219.97	Dominated by Solifenacin
Darifenacin	0.690	$477.99	$65,505.74	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutinin ER	0.693	$646.26	$66,203.11	Dominated by Solifenacin
Oxybutinin transdermal	0.690	$525.71	$70,089.98	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutinin gel	0.690	$554.65	$74,210.64	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutinin transdermal
Tolterodine ER	0.690	$540.90	$74,565.80	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutinin transdermal
Tolterodine IR	0.690	$540.83	$75,223.38	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutinin transdermal

Exhibit 57: Assuming OAB symptoms resolve in 7.12% of patients over the year.

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.684	$0.00	$0.00	$0.00
Solifenacin	0.694	$186.96	$18,979.75	$18,979.75
Dominated				
Oxybutinin IR	0.690	$144.17	$27,286.43	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.693	$462.91	$51,135.87	Dominated by Solifenacin
Trospium	0.693	$441.91	$53,120.14	Dominated by Solifenacin
Fesoterodine	0.692	$441.43	$56,114.83	Dominated by Solifenacin
Darifenacin	0.692	$475.83	$65,405.97	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutinin ER	0.694	$644.05	$66,132.34	Dominated by Solifenacin
Oxybutinin transdermal	0.692	$523.50	$70,009.76	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutinin gel	0.692	$552.44	$74,142.84	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutinin transdermal
Tolterodine ER	0.692	$538.68	$74,497.08	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutinin

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
				transdermal
Tolterodine IR	0.692	$538.62	$75,156.14	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutinin transdermal

Exhibit 58: Using alternative utilities derived using the EQ-5D from Desroziers et al.

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.692	$0.00	$0.00	$0.00
Solifenacin	0.700	$187.78	$22,576.49	$22,576.49
Dominated				
Oxybutinin IR	0.696	$145.36	$33,442.44	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.700	$464.08	$59,763.60	Dominated by Solifenacin
Trospium	0.699	$442.69	$63,600.77	Dominated by Solifenacin
Fesoterodine	0.699	$442.24	$66,988.76	Dominated by Solifenacin
Darifenacin	0.698	$476.93	$78,268.93	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutinin ER	0.700	$645.17	$78,642.85	Dominated by Solifenacin
Oxybutinin transdermal	0.699	$524.62	$81,267.27	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutinin gel	0.698	$553.56	$87,513.19	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutinin transdermal
Tolterodine ER	0.698	$539.81	$87,697.37	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutinin transdermal
Tolterodine IR	0.698	$539.74	$89,205.07	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutinin transdermal

Exhibit 59: Using alternative utilities derived using the OAB-5D from Desroziers et al.

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.665	$0.00	$0.00	$0.00
Solifenacin	0.679	$187.78	$13,571.45	$13,571.45
Dominated				
Oxybutinin IR	0.673	$145.36	$18,549.11	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.677	$464.08	$36,994.98	Dominated by Solifenacin
Trospium	0.676	$442.69	$38,070.91	Dominated by Solifenacin
Fesoterodine	0.676	$442.24	$39,753.28	Dominated by Solifenacin
Darifenacin	0.675	$476.93	$46,044.33	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutinin ER	0.678	$645.17	$47,062.91	Dominated by Solifenacin

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Oxybutinin transdermal	0.675	$524.62	$50,583.96	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutinin gel	0.675	$553.56	$53,135.58	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Tolterodine ER	0.675	$539.81	$53,291.25	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutinin transdermal
Tolterodine IR	0.675	$539.74	$53,346.62	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutinin transdermal

Exhibit 60: Assuming a disutility of zero for adverse events

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.684	$0.00	$0.00	$0.00
Solifenacin	0.694	$187.78	$17,719.09	$17,719.09
Dominated				
Oxybutynin IR	0.691	$145.36	$21,505.55	Subject to extended dominance through No therapy and Solifenacin
Trospium	0.693	$442.69	$49,767.37	Dominated by Solifenacin
Mirabegron	0.693	$464.08	$50,152.73	Dominated by Solifenacin
Fesoterodine	0.693	$442.24	$50,831.65	Dominated by Solifenacin
Darifenacin	0.692	$476.93	$58,032.75	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin ER	0.694	$645.17	$61,277.20	Dominated by Solifenacin
Oxybutynin transdermal	0.692	$524.62	$68,709.54	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin
Tolterodine IR	0.692	$539.74	$68,729.41	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin
Oxybutynin gel	0.692	$553.56	$70,086.63	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin
Tolterodine ER	0.692	$539.81	$70,141.36	Dominated by Tolterodine IR, Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin

Exhibit 61: Assuming a disutility of -0.1 for adverse events

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.683	$0.00	$0.00	$0.00
Solifenacin	0.692	$187.78	$22,029.27	$22,029.27
Mirabegron	0.692	$464.08	$53,193.27	$1,379,178.60
Dominated				
Oxybutynin IR	0.686	$145.36	$54,578.95	Subject to extended dominance through No therapy and Solifenacin, No therapy and Mirabegron
Trospium	0.690	$442.69	$60,639.19	Dominated by Solifenacin
Fesoterodine	0.690	$442.24	$69,265.62	Dominated by Solifenacin

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Oxybutynin transdermal	0.690	$524.62	$72,602.29	Dominated by Solifenacin, Trospium, Mirabegron
Oxybutynin ER	0.692	$645.17	$77,277.80	Dominated by Solifenacin, Mirabegron
Oxybutynin gel	0.690	$553.56	$82,890.64	Dominated by Solifenacin, Trospium, Mirabegron, Oxybutynin transdermal
Tolterodine ER	0.690	$539.81	$84,002.36	Dominated by Solifenacin, Trospium, Mirabegron, Oxybutynin transdermal
Darifenacin	0.689	$476.93	$85,053.59	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Tolterodine IR	0.689	$539.74	$90,515.32	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal

Exhibit 62: Reduced cost of darifenacin to 25% of current branded product

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.684	$0.00	$0.00	$0.00
Solifenacin	0.693	$187.78	$19,049.70	$19,049.70
Dominated				
Darifenacin	0.691	$169.68	$23,287.55	Subject to extended dominance through No therapy and Solifenacin, Oxybutinin IR and Solifenacin
Oxybutinin IR	0.689	$145.36	$27,442.19	Subject to extended dominance through No therapy and Darifenacin, No therapy and Solifenacin
Mirabegron	0.693	$464.08	$51,197.47	Dominated by Solifenacin
Trospium	0.692	$442.69	$53,170.58	Dominated by Solifenacin
Fesoterodine	0.691	$442.24	$56,168.19	Dominated by Solifenacin
Oxybutinin ER	0.693	$645.17	$66,168.22	Dominated by Solifenacin
Oxybutinin transdermal	0.691	$524.62	$70,050.41	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutinin gel	0.691	$553.56	$74,177.15	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutinin transdermal
Tolterodine ER	0.691	$539.81	$74,531.85	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutinin transdermal
Tolterodine IR	0.691	$539.74	$75,190.16	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutinin transdermal

Exhibit 63: Reduced cost of oxybutynin ER to 25% of current branded product

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.684	$0.00	$0.00	$0.00
Solifenacin	0.693	$187.78	$19,049.70	$19,049.70
Dominated				
Oxybutinin ER	0.693	$215.11	$22,061.83	Dominated by Solifenacin

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Oxybutinin IR	0.689	$145.36	$27,442.19	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.693	$464.08	$51,197.47	Dominated by Oxybutinin ER, Solifenacin
Trospium	0.692	$442.69	$53,170.58	Dominated by Oxybutinin ER, Solifenacin
Fesoterodine	0.691	$442.24	$56,168.19	Dominated by Oxybutinin ER, Solifenacin
Darifenacin	0.691	$476.93	$65,456.58	Dominated by Oxybutinin ER, Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutinin transdermal	0.691	$524.62	$70,050.41	Dominated by Oxybutinin ER, Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutinin gel	0.691	$553.56	$74,177.15	Dominated by Oxybutinin ER, Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutinin transdermal
Tolterodine ER	0.691	$539.81	$74,531.85	Dominated by Oxybutinin ER, Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutinin transdermal
Tolterodine IR	0.691	$539.74	$75,190.16	Dominated by Oxybutinin ER, Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutinin transdermal

Exhibit 64: Reduced cost of oxybutynin transdermal to 25% of current branded product

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.684	$0.00	$0.00	$0.00
Solifenacin	0.693	$187.78	$19,049.70	$19,049.70
Dominated				
Oxybutinin transdermal	0.691	$184.98	$24,698.99	Subject to extended dominance through No therapy and Solifenacin, Oxybutinin IR and Solifenacin
Oxybutinin IR	0.689	$145.36	$27,442.19	Subject to extended dominance through No therapy and Oxybutinin transdermal, No therapy and Solifenacin
Mirabegron	0.693	$464.08	$51,197.47	Dominated by Solifenacin
Trospium	0.692	$442.69	$53,170.58	Dominated by Solifenacin
Fesoterodine	0.691	$442.24	$56,168.19	Dominated by Solifenacin
Darifenacin	0.691	$476.93	$65,456.58	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutinin transdermal
Oxybutinin ER	0.693	$645.17	$66,168.22	Dominated by Solifenacin
Oxybutinin gel	0.691	$553.56	$74,177.15	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutinin transdermal
Tolterodine ER	0.691	$539.81	$74,531.85	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutinin transdermal
Tolterodine IR	0.691	$539.74	$75,190.16	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutinin transdermal

Exhibit 65: Reduced cost of oxybutynin gel to 25% of current branded product

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.684	$0.00	$0.00	$0.00
Solifenacin	0.693	$187.78	$19,049.70	$19,049.70
Dominated				
Oxybutinin gel	0.691	$192.21	$25,756.19	Dominated by Solifenacin
Oxybutinin IR	0.689	$145.36	$27,442.19	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.693	$464.08	$51,197.47	Dominated by Solifenacin
Trospium	0.692	$442.69	$53,170.58	Dominated by Solifenacin
Fesoterodine	0.691	$442.24	$56,168.19	Dominated by Solifenacin
Darifenacin	0.691	$476.93	$65,456.58	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutinin gel
Oxybutinin ER	0.693	$645.17	$66,168.22	Dominated by Solifenacin
Oxybutinin transdermal	0.691	$524.62	$70,050.41	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Tolterodine ER	0.691	$539.81	$74,531.85	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutinin transdermal, Oxybutinin gel
Tolterodine IR	0.691	$539.74	$75,190.16	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutinin transdermal, Oxybutinin gel

Exhibit 66: Reduced cost of Tolterodine ER to 25% of current branded product

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.684	$0.00	$0.00	$0.00
Solifenacin	0.693	$187.78	$19,049.70	$19,049.70
Dominated				
Tolterodine ER	0.691	$188.77	$26,064.02	Dominated by Solifenacin
Oxybutynin IR	0.689	$145.36	$27,442.19	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.693	$464.08	$51,197.47	Dominated by Solifenacin
Trospium	0.692	$442.69	$53,170.58	Dominated by Solifenacin
Fesoterodine	0.691	$442.24	$56,168.19	Dominated by Solifenacin
Darifenacin	0.691	$476.93	$65,456.58	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxbutynin ER	0.693	$645.17	$66,168.22	Dominated by Solifenacin
Oxbutynin transdermal	0.691	$524.62	$70,050.41	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxbutynin gel	0.691	$553.56	$74,177.15	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxbutynin transdermal
Tolterodine IR	0.691	$539.74	$75,190.16	Dominated by Tolterodine ER, Solifenacin, Fesoterodine,

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
				Trospium, Mirabegron, Darifenacin, Oxbutynin transdermal

Exhibit 67: Reduced cost of fesoterodine to 25% of branded product

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.684	$0.00	$0.00	$0.00
Solifenacin	0.693	$187.78	$19,049.70	$19,049.70
Dominated				
Fesoterodine	0.691	$154.55	$19,629.20	Subject to extended dominance through No therapy and Solifenacin
Oxybutinin IR	0.689	$145.36	$27,442.19	Subject to extended dominance through No therapy and Fesoterodine, No therapy and Solifenacin
Mirabegron	0.693	$464.08	$51,197.47	Dominated by Solifenacin
Trospium	0.692	$442.69	$53,170.58	Dominated by Solifenacin
Darifenacin	0.691	$476.93	$65,456.58	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutinin ER	0.693	$645.17	$66,168.22	Dominated by Solifenacin
Oxybutinin transdermal	0.691	$524.62	$70,050.41	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutinin gel	0.691	$553.56	$74,177.15	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutinin transdermal
Tolterodine ER	0.691	$539.81	$74,531.85	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutinin transdermal
Tolterodine IR	0.691	$539.74	$75,190.16	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutinin transdermal

Exhibit 68: Reduced cost of trospium to 25% of current branded product

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.684	$0.00	$0.00	$0.00
Trospium	0.692	$156.31	$18,773.85	$18,773.85
Solifenacin	0.693	$187.78	$19,049.70	$20,549.17
Dominated				
Oxybutinin IR	0.689	$145.36	$27,442.19	Subject to extended dominance through No therapy and Trospium, No therapy and Solifenacin
Mirabegron	0.693	$464.08	$51,197.47	Dominated by Solifenacin
Fesoterodine	0.691	$442.24	$56,168.19	Dominated by Solifenacin, Trospium
Darifenacin	0.691	$476.93	$65,456.58	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutinin ER	0.693	$645.17	$66,168.22	Dominated by Solifenacin

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Oxybutinin transdermal	0.691	$524.62	$70,050.41	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutinin gel	0.691	$553.56	$74,177.15	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutinin transdermal
Tolterodine ER	0.691	$539.81	$74,531.85	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutinin transdermal
Tolterodine IR	0.691	$539.74	$75,190.16	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutinin transdermal

Exhibit 69: Reduced cost of mirabegron to 25% of branded product

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.684	$0.00	$0.00	$0.00
Mirabegron	0.693	$164.53	$18,150.86	$18,150.86
Solifenacin	0.693	$187.78	$19,049.70	$29,326.36
Dominated				
Oxybutinin IR	0.689	$145.36	$27,442.19	Subject to extended dominance through No therapy and Mirabegron, No therapy and Solifenacin
Trospium	0.692	$442.69	$53,170.58	Dominated by Solifenacin, Mirabegron
Fesoterodine	0.691	$442.24	$56,168.19	Dominated by Solifenacin, Mirabegron
Darifenacin	0.691	$476.93	$65,456.58	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutinin ER	0.693	$645.17	$66,168.22	Dominated by Solifenacin
Oxybutinin transdermal	0.691	$524.62	$70,050.41	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutinin gel	0.691	$553.56	$74,177.15	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutinin transdermal
Tolterodine ER	0.691	$539.81	$74,531.85	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutinin transdermal
Tolterodine IR	0.691	$539.74	$75,190.16	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutinin transdermal

Exhibit 70: Incorporating the cost of incontinence pad within the analysis.

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.684	$348.03	$0.00	$0.00
Solifenacin	0.693	$446.72	$10,012.11	$10,012.11
Dominated				
Oxybutynin IR	0.689	$433.79	$16,190.78	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.693	$731.09	$42,259.29	Dominated by Solifenacin
Trospium	0.692	$723.39	$45,084.71	Dominated by Solifenacin

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Fesoterodine	0.691	$719.07	$47,125.37	Dominated by Solifenacin
Darifenacin	0.691	$757.55	$56,204.61	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin ER	0.693	$905.41	$57,164.31	Dominated by Solifenacin
Oxybutynin transdermal	0.691	$802.11	$60,631.51	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin gel	0.691	$835.68	$65,344.19	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal
Tolterodine ER	0.691	$821.61	$65,387.46	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal
Tolterodine IR	0.691	$821.97	$66,023.46	Dominated by Tolterodine ER, Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal

Exhibit 71: Reduced cost of incontinence pads to $0.74 per pad

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.684	$289.37	$0.00	$0.00
Solifenacin	0.693	$403.08	$11,535.30	$11,535.30
Dominated				
Oxybutynin IR	0.689	$385.18	$18,087.09	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.693	$686.09	$43,765.72	Dominated by Solifenacin
Trospium	0.692	$676.08	$46,447.50	Dominated by Solifenacin
Fesoterodine	0.691	$672.41	$48,649.44	Dominated by Solifenacin
Darifenacin	0.691	$710.25	$57,763.93	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin ER	0.693	$861.55	$58,681.83	Dominated by Solifenacin
Oxybutynin transdermal	0.691	$755.34	$62,218.97	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin gel	0.691	$788.13	$66,832.89	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal
Tolterodine ER	0.691	$774.11	$66,928.65	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal
Tolterodine IR	0.691	$774.40	$67,568.41	Dominated by Tolterodine ER, Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal

Exhibit 72: Increased cost of incontinence pads to a high of $1.83 per pad

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.684	$715.61	$0.00	$0.00
Solifenacin	0.693	$720.21	$466.80	$466.80

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Dominated				
Oxybutynin IR	0.689	$738.43	$4,307.28	Dominated by Solifenacin
Mirabegron	0.693	$1,013.10	$32,818.96	Dominated by Solifenacin
Trospium	0.692	$1,019.87	$36,544.59	Dominated by Solifenacin, Mirabegron
Fesoterodine	0.691	$1,011.45	$37,574.52	Dominated by Solifenacin
Darifenacin	0.691	$1,053.93	$46,432.87	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin ER	0.693	$1,180.27	$47,654.57	Dominated by Solifenacin
Oxybutynin transdermal	0.691	$1,095.19	$50,683.47	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Tolterodine ER	0.691	$1,119.24	$55,729.33	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal
Oxybutynin gel	0.691	$1,133.64	$56,015.00	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal
Tolterodine IR	0.691	$1,120.05	$56,341.78	Dominated by Tolterodine ER, Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal

Exhibit 73: Reduced time horizon to three months

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.719	$0.00	$0.00	$0.00
Solifenacin	0.720	$83.78	$46,131.90	$46,131.90
Oxybutynin ER	0.721	$260.74	$113,465.03	$367,161.62
Dominated				
Oxybutynin IR	0.719	$64.04	$103,298.14	Subject to extended dominance through No therapy and Solifenacin
Trospium	0.720	$186.99	$107,641.42	Dominated by Solifenacin
Mirabegron	0.720	$178.82	$107,899.13	Dominated by Solifenacin
Oxybutynin transdermal	0.720	$213.99	$150,094.22	Dominated by Solifenacin, Trospium, Mirabegron
Fesoterodine	0.720	$179.48	$167,803.82	Dominated by Solifenacin, Mirabegron
Oxybutynin gel	0.720	$225.22	$183,509.96	Dominated by Solifenacin, Trospium, Mirabegron, Oxybutynin transdermal
Tolterodine ER	0.720	$219.88	$197,284.25	Dominated by Solifenacin, Trospium, Mirabegron, Oxybutynin transdermal
Tolterodine IR	0.720	$219.86	$227,744.13	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal
Darifenacin	0.719	$190.31	$288,595.31	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron

Exhibit 74: Patients switch to solifenacin as second line therapy rather than tolterodine ER

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
No therapy	0.684	$0.00	$0.00	$0.00
Solifenacin	0.694	$175.51	$17,678.07	$17,678.07
Dominated				
Oxybutynin IR	0.689	$106.55	$19,246.19	Subject to extended dominance through No therapy and Solifenacin
Mirabegron	0.693	$446.55	$48,720.85	Dominated by Solifenacin
Trospium	0.692	$426.70	$50,677.54	Dominated by Solifenacin
Fesoterodine	0.692	$427.95	$53,785.74	Dominated by Solifenacin, Trospium
Darifenacin	0.691	$457.50	$61,829.78	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Tolterodine ER	0.692	$509.88	$61,905.99	Dominated by Solifenacin, Trospium, Mirabegron
Oxybutynin ER	0.694	$622.75	$63,017.34	Dominated by Solifenacin
Oxybutynin transdermal	0.691	$502.20	$65,897.50	Dominated by Solifenacin, Fesoterodine, Trospium, Mirabegron
Oxybutynin gel	0.691	$531.14	$69,938.17	Dominated by Tolterodine ER, Solifenacin, Fesoterodine, Trospium, Mirabegron, Oxybutynin transdermal
Tolterodine IR	0.691	$517.32	$70,768.01	Dominated by Tolterodine ER, Solifenacin, Fesoterodine, Trospium, Mirabegron, Darifenacin, Oxybutynin transdermal

Appendix C – Budget Impact Analysis

Research Question

What is the budget impact of alternative policies for reimbursing pharmacotherapies in the treatment of OAB syndrome?

Reimbursement Based Economic Assessment: Methods

An applied, policy-oriented economic model focusing on financial impact was developed to facilitate consideration of alternative reimbursement strategies for available pharmacologic treatments in the management of adults with overactive bladder symptoms. Utilization data for anticholinergic OAB medications (darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium) were provided by the Ontario Public Drug Program (OPDP) from January 1, 2000 to September 30, 2015; data relating to the use of mirabegron (beta-3 adrenergic agonist) was only available for the period spanning May 28, 2015 to September 30, 2015 as this treatment was not previously covered on the Ontario Drug Benefit (ODB) formulary.

The number of users per quarter of anticholinergic medications and mirabegron were predicted for the next 36 consecutive months (from 2016 to 2018) using time-series analysis. Namely, four models were used to forecast the number of users of anticholinergic agents.

1. A linear model whereby the number of users was assumed to increase by the same amount each year and also increase with each new OAB medication covered under OPDP.
2. An exponential model where an exponential relationship between number of users and time and the number of OAB medications covered under OPDP was assumed.
3. A power model that allowed a non-linear relationship between time and number of users, and included the number of OAB medications covered by OPDP.
4. A constant growth model that assumed a constant percentage increase in the number of users, with additional coverage of new OAB medications also leading to a percentage increase.

All of the models considered the following variables: quarter (i.e. January 1-March 31, 2000 was quarter 1, April 1-June 30, 2000 was quarter 2, etc.), the number of available OAB medications per drug class covered by OPDP, and a variable relating to the availability of mirabegron. Each model was examined for seasonal effects based on absolute and Winters' seasonal effects calculations. Moreover, the most suitable combination of independent variables and inclusion of seasonal effects were selected for each model based on the Bayesian information criterion (BIC). Prediction models were developed for two age groups, as per data provided by OPDP: users of OAB medications aged less than 65 years and those who were 65 years and older. The final models were chosen based on best fit parameters, which were calculated as part of the budget impact model building (see Appendix C1: Model Details). More specifically, the linear model with seasonal effects was chosen for the under 65 age group, and the power model with seasonal effects was chosen for the 65 and over age group.

Once forecasted estimates for the number of users were obtained for years 2016-2018, these values were then transformed to annual expenditure estimates; this was done by multiplying the total number of predicted users per year by the average units per user per quarter and the average cost per unit per quarter representing the last four quarters of available raw data,

allowing for the availability of generic formulations (Status Quo). Predicted expenditure under alternative reimbursement strategies were then estimated. Exhibit 75, Exhibit 76, and Exhibit 77 outline the alternative reimbursement strategies being considered for this drug class, assuming either no change or different levels of change in mirabegron prescribing trends for the period spanning years 2016 to 2018.

Data were only available for mirabegron for the period May 28 to September 30 2015. Given this, we made three separate assumptions around use of mirabegron: no increase in use for the initial period, a 10% increase in use each year, and a 20% increase in use each year. For the latter two assumptions, the forecasted use of anticholinergic agents would change based on the increased use of mirabegron.

Exhibit 75: Alternative reimbursement strategies for OAB medications covered by OPDP assuming no change in mirabegron prescribing for years 2016-2018.

	Strategy[†]	Assumptions
1a.	Status quo: no change. General benefit (GB): oxybutynin IR Limited use (LU): currently covered agents (DAR, FES, SOL, TOL, TRO, MYR, BTX)	▪ Use current ACh utilization trends to forecast costs for 2016-2018. ▪ Extrapolate current usage for mirabegron (125 days) to 1 year for 2015, and assume no change in expenditure for 2016-2018.
1b.	Same as 1a EXCEPT: LU listing for Ditropan XL, Gelnique, Oxytrol	▪ Assume 5% of current ACh users (DAR, FES, OXY, SOL, TOL, TRO) move to Ditropan XL, Gelnique, and Oxytrol (equal amongst this).
2a.	ENFORCED STEP THERAPY General benefit (GB): oxybutynin IR Limited use (LU): currently covered agents	▪ Assume the following percentage reductions in users for therapies: DAR (34.6%), FES (35.0%), SOL (30.4%), TOL (43.1%), TRO (40.7%), MYR (36.8%); then assume these users move to OXY. ▪ *Assume no increase in time on all OAB agents.*
2b.	ENFORCED STEP THERAPY Same as 2a EXCEPT: LU listing for Ditropan XL, Gelnique, Oxytrol	▪ Assume the following percentage reductions in users for therapies: DAR (34.6%), FES (35.0%), SOL (30.4%), TOL (43.1%), TRO (40.7%), MYR (36.8%); then assume these users move to OXY. ▪ Assume 5% of remaining ACh users move to Ditropan XL, Gelnique, and Oxytrol (equal amongst this).
3a.	ENFORCED STEP THERAPY General benefit (GB): oxybutynin IR Limited use (LU): currently covered agents	▪ Assume an increase in oxybutynin users by the following percentage of the forecasted users for other therapies: DAR (34.6%), FES (35.0%), SOL (30.4%), TOL (43.1%), TRO (40.7%), MYR (36.8%). ▪ *Assume **no decrease** in use of other OAB therapies.*
3b.	ENFORCED STEP THERAPY Same as 3a EXCEPT: LU listing for Ditropan XL, Gelnique, Oxytrol	▪ Assume an increase in oxybutynin users by the following percentage of the forecasted users for other therapies: DAR (34.6%), FES (35.0%), SOL (30.4%), TOL (43.1%), TRO (40.7%), MYR (36.8%). ▪ *Assume **no decrease** in use of other OAB therapies.*

	Strategy†	Assumptions
		▪ Assume 5% of remaining ACh users move to Ditropan XL, Gelnique, and Oxytrol (equal amongst this).
4a.	GB listing for generic products including oxybutynin, tolterodine IR, and solifenacin. LU listing for currently covered agents except tolterodine IR and solifenacin	▪ Assume the following decline in oxybutynin users: 22.2% (<65 yrs) and 52.4% (≥65 yrs); then assume: (1) 46% and 54% of users in the <65 years age group move to tolterodine and solifenacin, respectively, and (2) 44.7% and 55.3% of users in the ≥65 years age group move to tolterodine and solifenacin, respectively.
4b.	Same as 4a EXCEPT: LU listing for Ditropan XL, Gelnique, Oxytrol	▪ Assume 5% of current ACh users (DAR, FES, OXY, SOL, TOL, TRO) move to Ditropan XL, Gelnique, and Oxytrol (equal amongst this). ▪ Assume the following decline in oxybutynin users: 22.2% (<65 yrs) and 52.4% (≥65 yrs); then assume: (1) 46% and 54% of users in the <65 years age group move to tolterodine and solifenacin, respectively, and (2) 44.7% and 55.3% of users in the ≥65 years age group move to tolterodine and solifenacin, respectively.
5a.	GB listing for OXY and SOL and LU listing for all other currently covered agents	▪ Assume the following decline in oxybutynin users: 22.2% (<65 yrs) and 52.4% (≥65 yrs); then assume all those who would not take oxybutynin move to solifenacin.
5b.	GB listing for SOL and LU listing for all other currently covered agents	▪ Assume 100% of current oxybutynin users move to solifenacin.

Note: ACh=Anticholinergic medications, BTX = botulinum toxin A, DAR=darifenacin, FES=fesoterodine, MYR=mirabegron, OXY=oxybutynin, SOL=solifenacin, TOL=tolterodine, TRO=trospium

†All reimbursement strategies assume that the price of solifenacin is reduced to 25% of the brand reference product.

Exhibit 76: Alternative reimbursement strategies for OAB medications covered by OPDP assuming 10% increase in mirabegron prescribing per annum for years 2016-2018.

	Strategy†	Assumptions
1c.	Status quo (base-case): No change to current GB listing for OXY IR and LU listing for currently covered agents, and a 10% increase in mirabegron use per year.	▪ Use current ACh utilization trends to forecast costs for 2016-2018. ▪ Extrapolate current usage for mirabegron (125 days) to 1 year for 2015; then assume increase in mirabegron use by 10% each year for 2016-2018.
2c.	Same as 2a EXCEPT: 10% increase in mirabegron use	▪ Extrapolate current usage for mirabegron (125 days) to 1 year for 2015; then assume increase in mirabegron use by 10% each year for 2016-2018. ▪ Assume the following percentage reductions in users for therapies: DAR (34.6%), FES (35.0%), SOL (30.4%), TOL (43.1%), TRO (40.7%), MYR (36.8%); then assume these users move to OXY.

	Strategy†	Assumptions
3c.	Same as 3a EXCEPT: 10% increase in mirabegron use	▪ Extrapolate current usage for mirabegron (125 days) to 1 year for 2015; then assume increase in mirabegron use by 10% each year for 2016-2018. ▪ Assume an increase in oxybutynin users by the following percentage of the forecasted users for other therapies: DAR (34.6%), FES (35.0%), SOL (30.4%), TOL (43.1%), TRO (40.7%), MYR (36.8%). ▪ *Assume **no decrease** in use of other OAB therapies.*
4c.	Same as 4a EXCEPT: 10% increase in mirabegron use	▪ Extrapolate current usage for mirabegron (125 days) to 1 year for 2015; then assume increase in mirabegron use by 10% each year for 2016-2018. ▪ Assume the following decline in oxybutynin users: 22.2% (<65 yrs) and 52.4% (≥65 yrs); then assume: (1) 46% and 54% of users in the <65 years age group move to tolterodine and solifenacin, respectively, and (2) 44.7% and 55.3% of users in the ≥65 years age group move to tolterodine and solifenacin, respectively.

Note: ACh=Anticholinergic medications, BTX = botulinum toxin A, DAR=darifenacin, FES=fesoterodine, MYR=mirabegron, OXY=oxybutynin, SOL=solifenacin, TOL=tolterodine, TRO=trospium
†All reimbursement strategies assume that the price of solifenacin is reduced to 25% of the brand reference product.

Exhibit 77: Alternative reimbursement strategies for OAB medications covered by OPDP assuming 20% increase in mirabegron prescribing per annum for years 2016-2018.

	Strategy†	Assumptions
1d.	Status quo (base-case): No change to current GB listing for OXY IR and LU listing for currently covered agents, and a 20% increase in mirabegron use per year.	▪ Use current ACh utilization trends to forecast costs for 2016-2018. ▪ Extrapolate current usage for mirabegron (125 days) to 1 year for 2015; then assume increase in mirabegron use by 20% each year for 2016-2018.
2d.	Same as 2a EXCEPT: 20% increase in mirabegron use	▪ Extrapolate current usage for mirabegron (125 days) to 1 year for 2015; then assume increase in mirabegron use by 10% each year for 2016-2018. ▪ Assume the following percentage reductions in users for therapies: DAR (34.6%), FES (35.0%), SOL (30.4%), TOL (43.1%), TRO (40.7%), MYR (36.8%); then assume these users move to OXY.
3d.	Same as 3a EXCEPT: 20% increase in mirabegron use	▪ Extrapolate current usage for mirabegron (125 days) to 1 year for 2015; then assume increase in mirabegron use by 10% each year for 2016-2018. ▪ Assume an increase in oxybutynin users by the following percentage of the forecasted

	Strategy†	Assumptions
		users for other therapies: DAR (34.6%), FES (35.0%), SOL (30.4%), TOL (43.1%), TRO (40.7%), MYR (36.8%). ▪ *Assume **no decrease** in use of other OAB therapies.*
4d.	Same as 4a EXCEPT: 20% increase in mirabegron use	▪ Extrapolate current usage for mirabegron (125 days) to 1 year for 2015; then assume increase in mirabegron use by 10% each year for 2016-2018. ▪ Assume the following decline in oxybutynin users: 22.2% (<65 yrs) and 52.4% (≥65 yrs); then assume: (1) 46% and 54% of users in the <65 years age group move to tolterodine and solifenacin, respectively, and (2) 44.7% and 55.3% of users in the ≥65 years age group move to tolterodine and solifenacin, respectively.

Note: ACh=Anticholinergic medications, BTX = botulinum toxin A, DAR=darifenacin, FES=fesoterodine, MYR=mirabegron, OXY=oxybutynin, SOL=solifenacin, TOL=tolterodine, TRO=trospium
†All reimbursement strategies assume that the price of solifenacin is reduced to 25% of the brand reference product.

Findings

Current Usage and Expenditure

For overactive bladder patients who were aged less than 65 years, the total average number of users, units, and prescriptions per quarter for OAB medications in Q4/2014 to Q3/2015 was 13,492, 1,551,402, and 69,216, respectively. For OAB patients aged 65 years and older, the total average number of users, units, and prescriptions per quarter for these medications in 2014-15 was 60,402, 5,906,714, and 200,861, respectively. Among both age groups, anticholinergic medications accounted for the majority of total OAB medication usage (84-91%), with oxybutynin as the most commonly prescribed anticholinergic agent among patients aged less than 65 years, and tolterodine as the most commonly prescribed agent among patients aged 65 years and older. Detailed information relating to the usage of currently available OAB medications is presented in Exhibit 78.

Exhibit 78: Average number of overactive bladder medication users, units, and prescriptions per quarter in 2014-15.

	Users		Units		Prescriptions	
	<65 yrs N (%)	**≥65 yrs N (%)**	**<65 yrs N (%)**	**≥65 yrs N (%)**	**<65 yrs N (%)**	**≥65 yrs N (%)**
Total	13492 (100%)	60402 (100%)	1551402 (100%)	5906714 (100%)	69216 (100%)	200861 (100%)
Anticholinergic agents	12307 (91%)	50625 (84%)	1474602 (95%)	5227049 (88%)	65762 (95%)	176601 (88%)
darifenacin	445 (3%)	2919 (5%)	42478 (3%)	274870 (5%)	2068 (3%)	10972 (5%)

	Users		Units		Prescriptions	
fesoterodine	1069 (8%)	6536 (11%)	87672 (6%)	555186 (9%)	5051 (7%)	22754 (11%)
oxybutynin	4833 (36%)	8239 (14%)	758481 (49%)	1074540 (18%)	28875 (42%)	27729 (14%)
solifenacin	2627 (19%)	14722 (24%)	232024 (15%)	1361360 (23%)	11789 (17%)	49955 (25%)
tolterodine	3280 (24%)	17772 (29%)	346277 (22%)	1899317 (32%)	17621 (25%)	63328 (32%)
trospium	55 (0%)	438 (1%)	7670 (0%)	61777 (1%)	358 (1%)	1864 (1%)
Beta-3 adrenergic agonists	1185 (9%)	9778 (16%)	76800 (5%)	679665 (12%)	3454 (5%)	24261 (12%)
mirabegron†	1185 (9%)	9778 (16%)	76800 (5%)	679665 (12%)	3454 (5%)	24261 (12%)

Note: Averages calculated using raw data from the last quarter (Q4) of 2014 to the third quarter of 2015.
†Available utilization data (125 days) was extrapolated to 1 year and then averaged over four quarters.

Since 2000, OPDP expenditure for OAB medications has increased among persons aged less than 65 years as well as those who were 65 years and older; however, the observed growth in spending was considerably greater among the elderly (65+) age group, which accounts for the majority of users of these medications. Namely, total spending among persons aged 65 years and over has risen from about $4.5 million in 2000 to over $31.3 million in 2014 (Exhibit 80). Conversely, total expenditure on OAB anticholinergic agents among patients aged less than 65 years has increased from approximately $1.0 million to $6.1 million from 2000 to 2014 (Exhibit 79). Given that mirabegron has been listed on the ODB formulary as a limited use benefit since May 2015, anticholinergic urologic agents have accounted to date for the majority of OPDP expenditure for OAB medications among all patient groups.

Exhibit 79: OPDP expenditure on OAB medications among patients aged less than 65 years from January 1, 2000 to September 30, 2015.

Year	Anticholinergic agents	Mirabegron	Total
2000	$1,019,622.24	$0.00	$1,019,622.24
2001	$1,338,534.09	$0.00	$1,338,534.09
2002	$1,610,003.27	$0.00	$1,610,003.27
2003	$1,867,769.25	$0.00	$1,867,769.25
2004	$2,277,364.19	$0.00	$2,277,364.19
2005	$2,683,306.35	$0.00	$2,683,306.35
2006	$3,071,126.91	$0.00	$3,071,126.91
2007	$3,382,230.81	$0.00	$3,382,230.81

Year	Anticholinergic agents	Mirabegron	Total
2008	$3,714,922.20	$0.00	$3,714,922.20
2009	$3,963,263.12	$0.00	$3,963,263.12
2010	$4,373,710.52	$0.00	$4,373,710.52
2011	$4,655,650.72	$0.00	$4,655,650.72
2012	$5,245,283.41	$0.00	$5,245,283.41
2013	$5,899,324.89	$0.00	$5,899,324.89
2014	$6,209,228.98	$0.00	$6,209,228.98
2015[†]	$4,681,583.50	$180,404.00	$4,861,987.50

[†]Total expenditure for anticholinergic medications represents the period from January 1, 2015 to September 30, 2015 (Q1 to Q3), and total expenditure for mirabegron represents the period from May 28, 2015 to September 30, 2015.

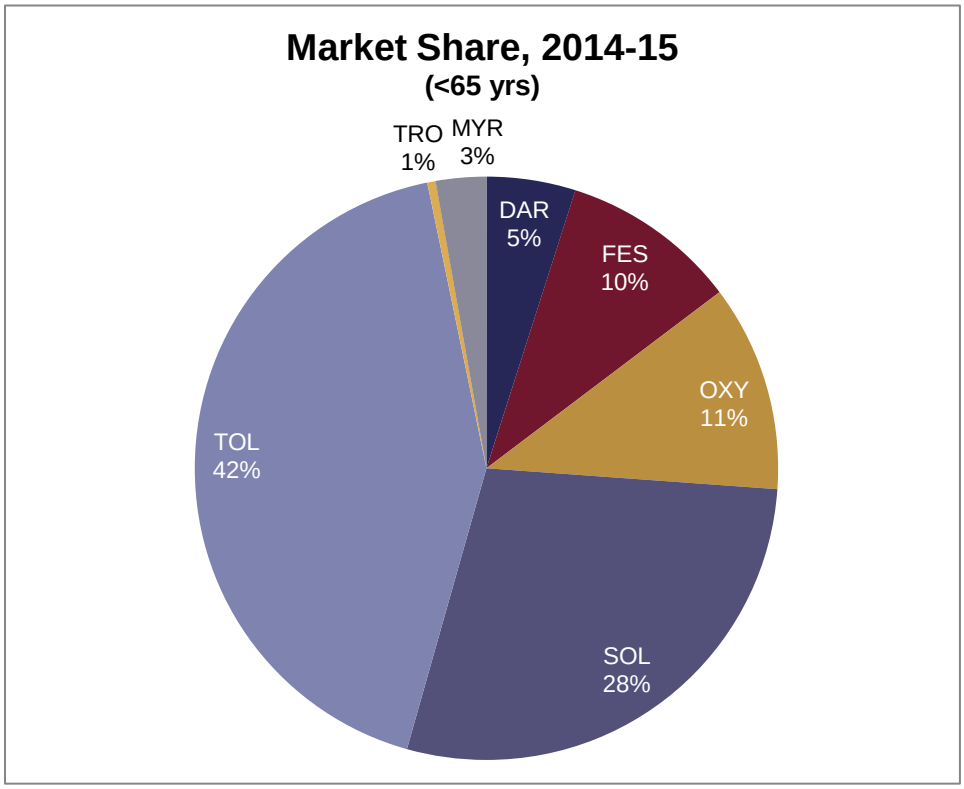
Exhibit 80: OPDP expenditure on OAB medications among patients aged 65 years and older from January 1, 2000 to September 30, 2015.

Year	Anticholinergic agents	Mirabegron	Total
2000	$4,566,103.32	$0.00	$4,566,103.32
2001	$6,740,839.91	$0.00	$6,740,839.91
2002	$8,347,995.64	$0.00	$8,347,995.64
2003	$9,639,655.31	$0.00	$9,639,655.31
2004	$11,739,140.46	$0.00	$11,739,140.46
2005	$13,557,117.87	$0.00	$13,557,117.87
2006	$15,644,042.53	$0.00	$15,644,042.53
2007	$17,559,475.33	$0.00	$17,559,475.33
2008	$19,097,800.14	$0.00	$19,097,800.14
2009	$20,543,834.95	$0.00	$20,543,834.95
2010	$22,049,149.78	$0.00	$22,049,149.78
2011	$22,892,397.48	$0.00	$22,892,397.48
2012	$26,964,796.82	$0.00	$26,964,796.82
2013	$29,722,993.71	$0.00	$29,722,993.71
2014	$31,330,100.95	$0.00	$31,330,100.95
2015[†]	$22,887,332.55	$1,372,886.69	$24,260,219.24

[†]Total expenditure for anticholinergic medications represents the period from January 1, 2015 to September 30, 2015 (Q1 to Q3), and total expenditure for mirabegron represents the period from May 28, 2015 to September 30, 2015.

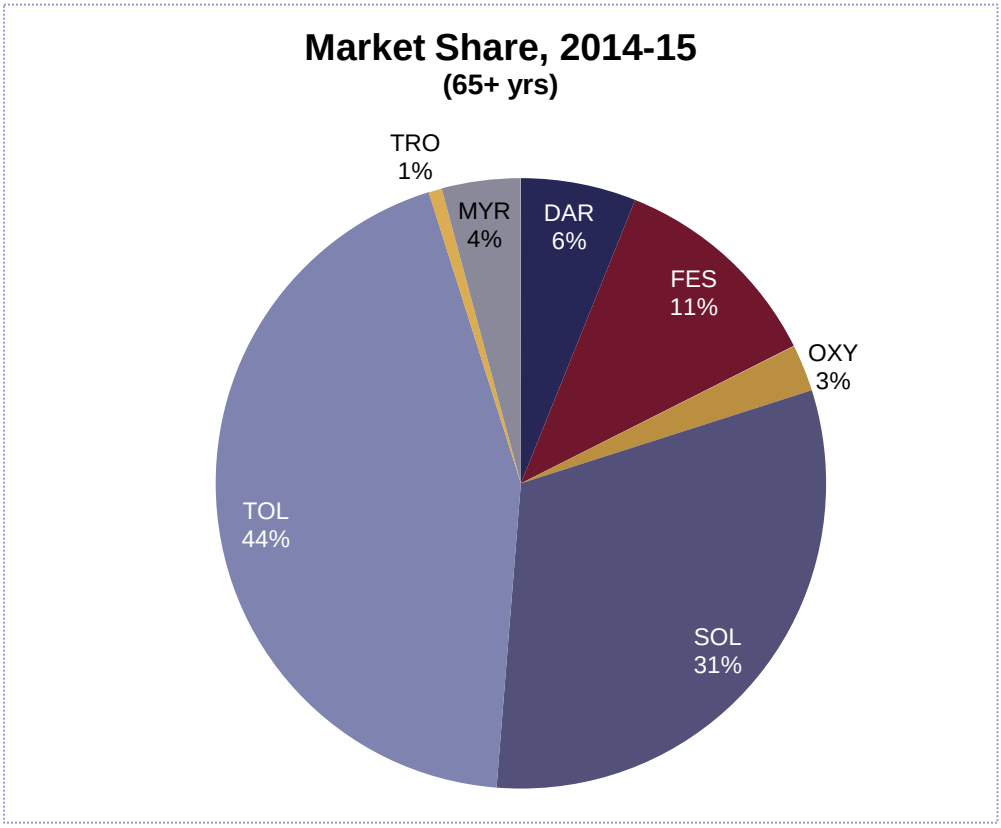
Based on expenditure in 2014-15, tolterodine held the largest market share among all currently available OAB medications for patients under age 65 (Exhibit 81) and for patients aged 65 years and older (Exhibit 82), with 42% and 44%, respectively. Conversely, anticholinergic agent trospium has the smallest market share (~1%) among both age groups during the same time period.

Exhibit 81: Market share of OAB medications for patients aged less than 65 years.



Note: Market share occupied by mirabegron (MYR) is based on currently available expenditure data obtained from OPDP (May 28, 2015 – September 30, 2015).

Exhibit 82: Market share of OAB medications for patients aged 65 years and older.



Note: Market share occupied by mirabegron (MYR) is based on currently available expenditure data obtained from OPDP (May 28, 2015 – September 30, 2015).

Forecasting expenditure

Given the anticipated generic availability of solifenacin by the end of 2015 and the significant price reduction (~25% of brand reference product) that is associated with its introduction, overall expenditure for OAB medications is expected to markedly decline over the next three years for all patient groups (Exhibit 83, Exhibit 84). Even though overall spending is likely to decrease, the number of users of OAB medications is expected to continue to grow. Accordingly, tolterodine is projected to account for the absolute growth in expenditure among anticholinergic medications from 2016 to 2018 for all age groups based on current trends. Conversely, the forecast in expenditure for beta-3 adrenergic agonist mirabegron remains unclear as a result of its recent addition to the ODB formulary and the uncertainty surrounding its future uptake.

If mirabegron prescribing were to increase by either 10% or 20% per annum from 2016 to 2018, the projected impact on overall OAB medication expenditure would be negligible

(assuming no change to current coverage of OAB medications). Tolterodine would still account for the absolute growth in expenditure among all OAB medications for all age groups based on current prescribing trends (see Exhibit 85, Exhibit 86, Exhibit 87, Exhibit 88)

Exhibit 83: Forecasted OAB medication expenditure for patients aged less than 65 years assuming no change in mirabegron prescribing (calibrated to actual data from 2014-15).

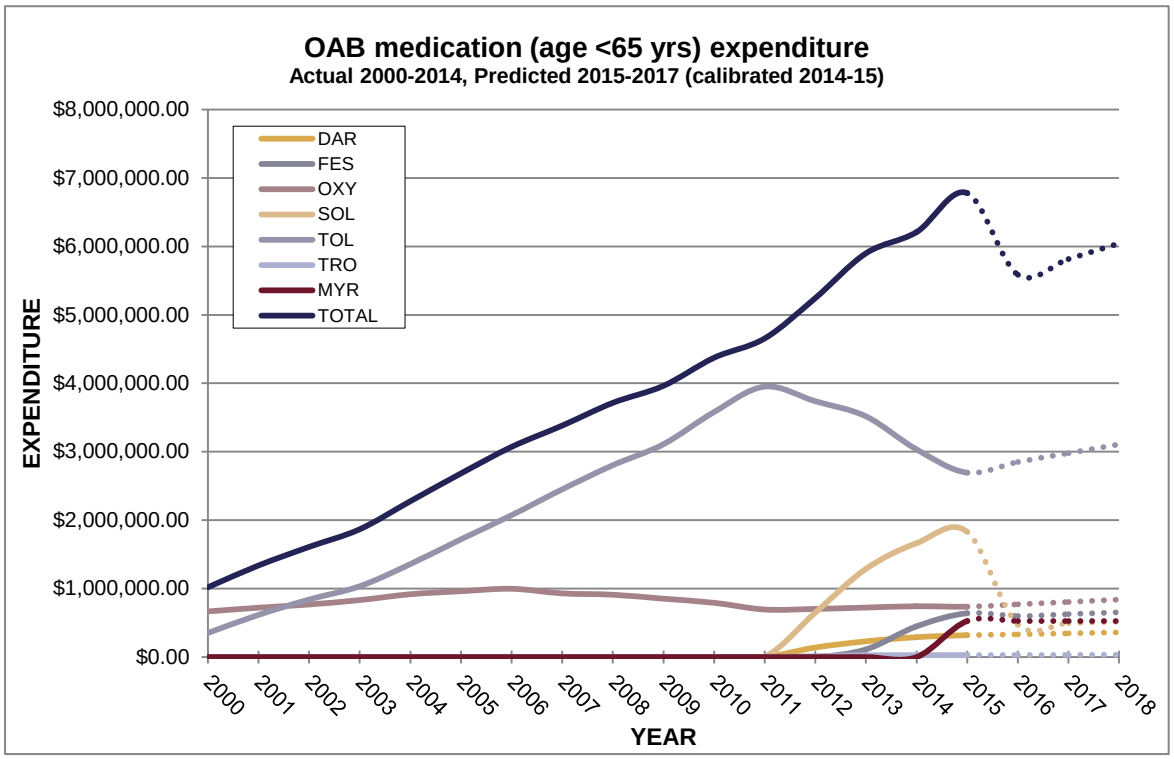


Exhibit 84: Forecasted OAB medication expenditure for patients aged 65 years and older assuming no change in mirabegron prescribing (calibrated to actual data from 2014-15).

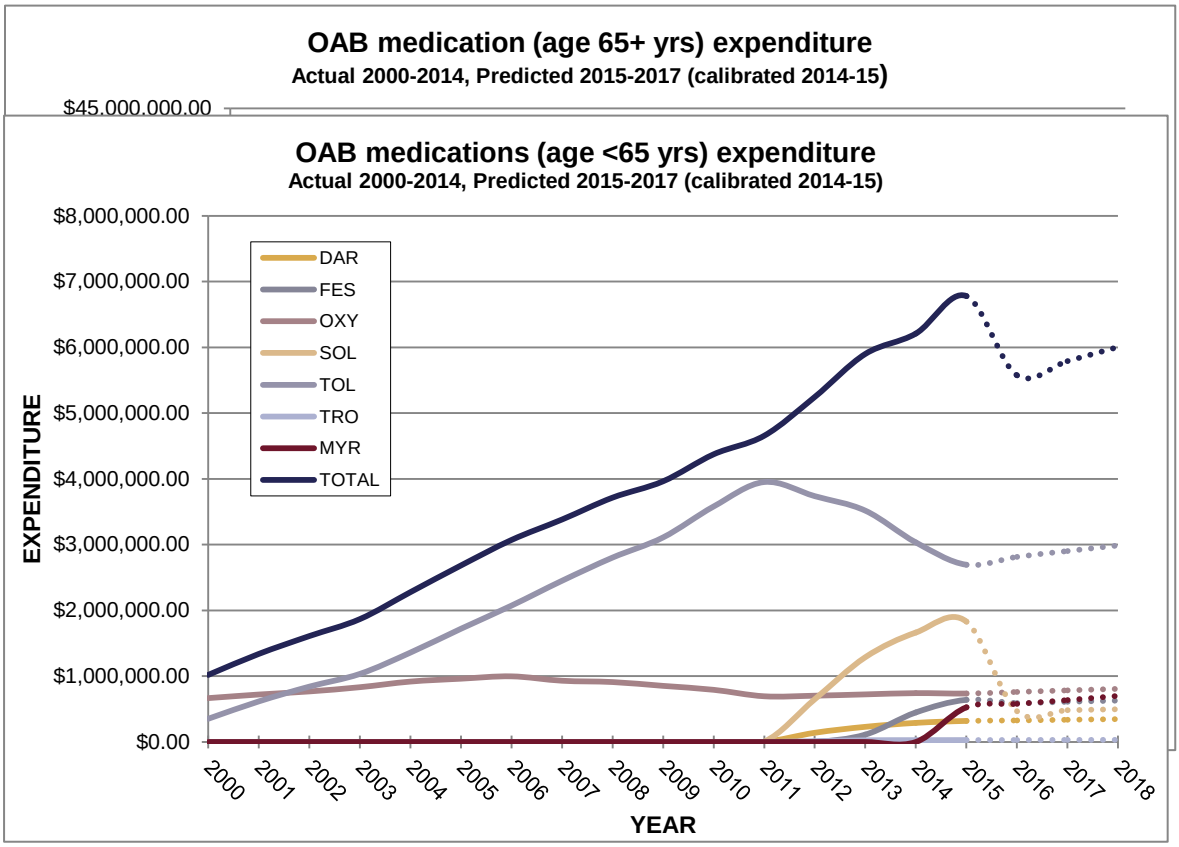


Exhibit 85: Forecasted OAB medication expenditure for patients aged less than 65 years assuming a 10% increase in mirabegron prescribing per annum (calibrated to actual data from 2014-15)

Exhibit 86: Forecasted OAB medication expenditure for patients aged 65 years and older assuming a 10% increase in mirabegron prescribing per annum (calibrated to actual data from 2014-15).

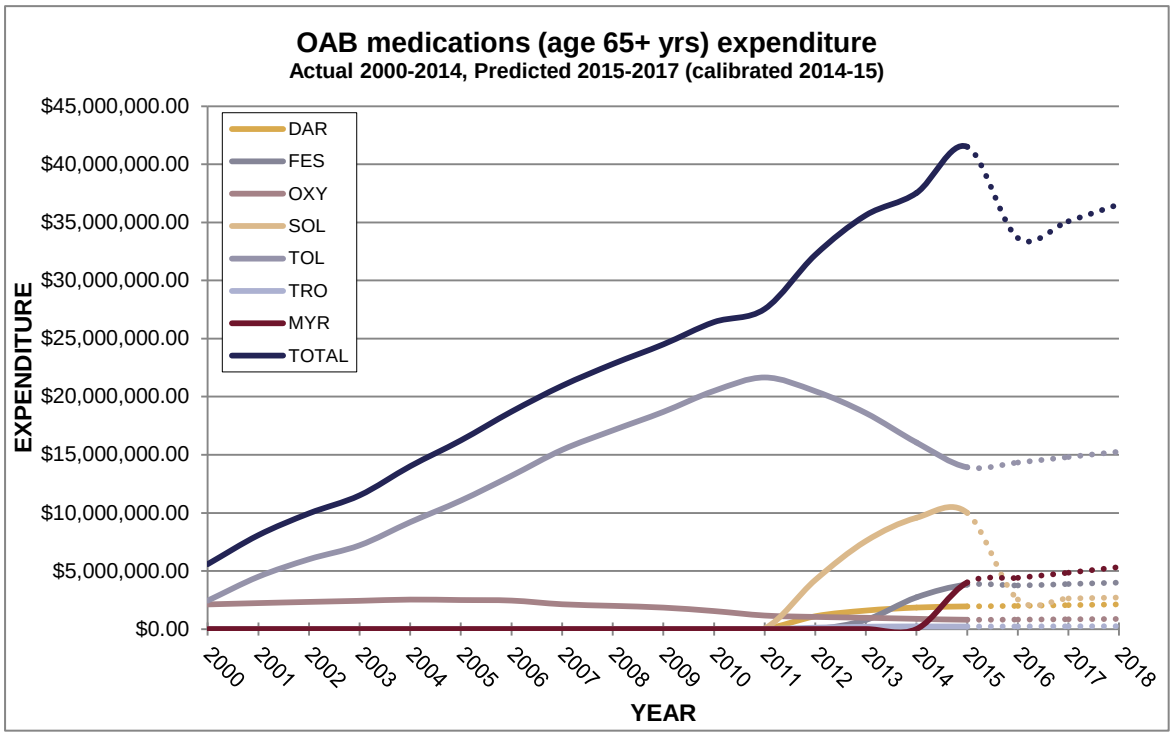


Exhibit 87: Forecasted OAB medication expenditure for patients aged less than 65 years assuming a 20% increase in mirabegron prescribing per annum (calibrated to actual data from 2014-15)

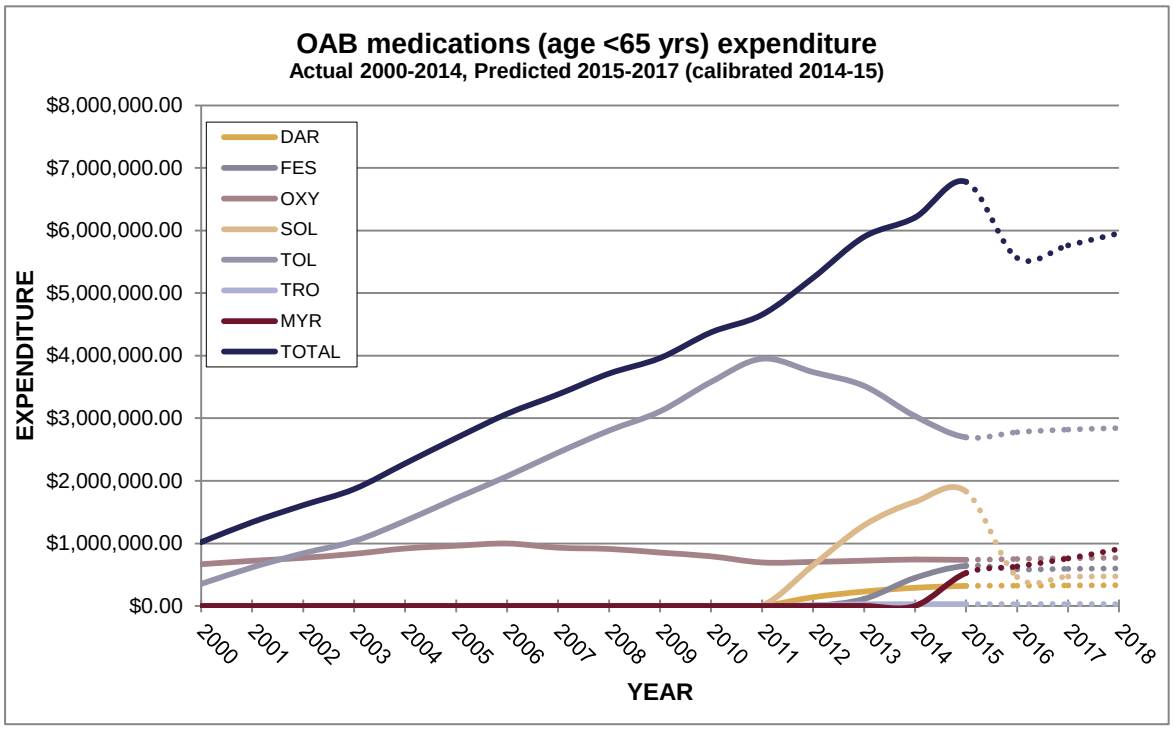
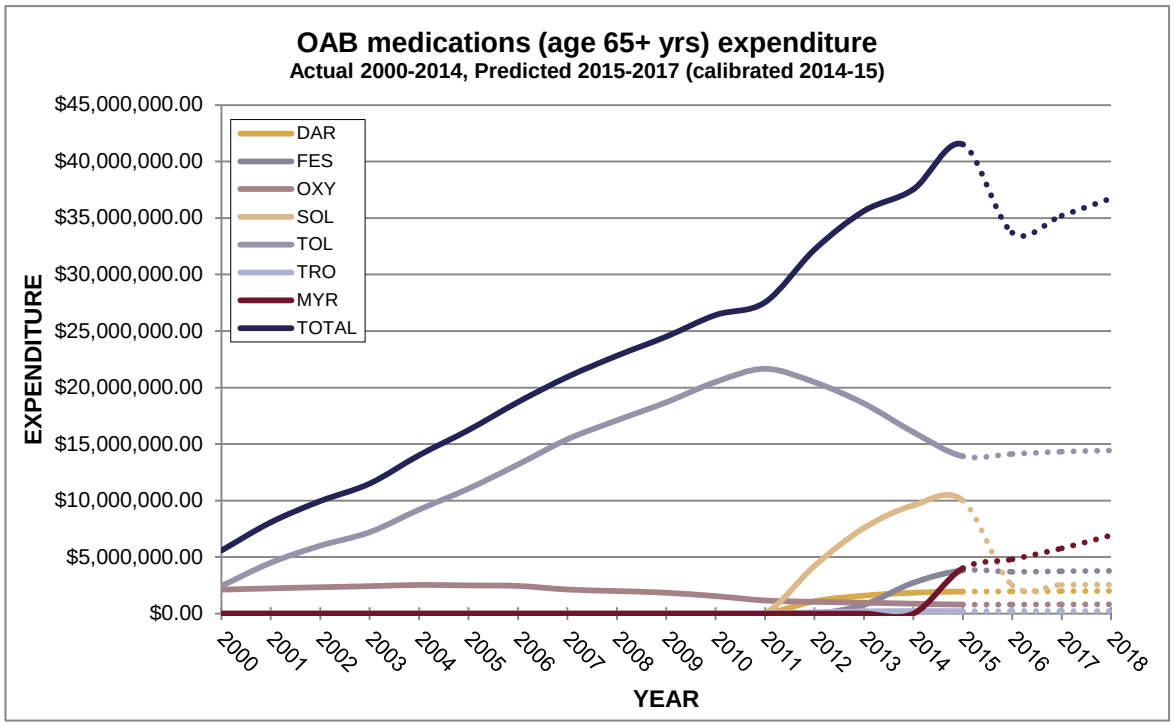


Exhibit 88: Forecasted OAB medication expenditure for patients aged 65 years and older assuming a 20% increase in mirabegron prescribing per annum (calibrated to actual data from 2014-15).



With the introduction of generic solifenacin by the end of 2015, but no other changes to current reimbursement for OAB medications, expenditure is expected to drop to about $6.0 million by 2018 for patients aged less than 65 years and to approximately $30.4 million for patients aged 65 years and older (Exhibit 89, Exhibit 90).

Exhibit 89: Forecasted expenditure for OAB medications for patients aged less than 65 years.

YEAR	OAB MEDICATION EXPENDITURE (<65 yrs)							
ACTUAL	**DAR**	**FES**	**OXY**	**SOL**	**TOL**	**TRO**	**MYR**	**TOTAL**
2000	$0	$0	$666,968	$0	$352,654	$0	$0	$1,019,622
2001	$0	$0	$721,757	$0	$616,777	$0	$0	$1,338,534
2002	$0	$0	$768,619	$0	$841,385	$0	$0	$1,610,003
2003	$0	$0	$832,946	$0	$1,034,823	$0	$0	$1,867,769
2004	$0	$0	$918,523	$0	$1,358,841	$0	$0	$2,277,364
2005	$0	$0	$962,172	$0	$1,721,135	$0	$0	$2,683,306
2006	$0	$0	$998,100	$0	$2,073,027	$0	$0	$3,071,127
2007	$0	$0	$931,259	$0	$2,450,972	$0	$0	$3,382,231
2008	$0	$0	$911,238	$0	$2,803,684	$0	$0	$3,714,922
2009	$0	$0	$853,142	$0	$3,110,121	$0	$0	$3,963,263
2010	$0	$0	$793,200	$0	$3,580,510	$0	$0	$4,373,711
2011	$2,078	$0	$695,109	$6,234	$3,951,928	$303	$0	$4,655,651
2012	$140,140	$0	$703,978	$650,070	$3,737,540	$13,556	$0	$5,245,283
2013	$230,600	$112,480	$723,849	$1,289,032	$3,516,927	$26,437	$0	$5,899,325
2014	$290,716	$449,528	$742,862	$1,664,051	$3,033,949	$28,123	$0	$6,209,229
2015[†]	$320,367	$640,927	$736,592	$1,830,255	$2,694,667	$29,338	$526,780	$6,778,925
PREDICTED								
2016	$331,833	$600,352	$770,756	$475,108	$2,850,447	$31,329	$526,780	$5,586,606
2017	$346,819	$627,465	$805,564	$496,564	$2,979,177	$32,744	$526,780	$5,815,113
2018	$361,805	$654,578	$840,372	$518,020	$3,107,906	$34,159	$526,780	$6,043,621

Note: DAR=darifenacin, FES=fesoterodine, OXY=oxybutynin, SOL=solifenacin, TOL=tolterodine, TRO=trospium, MYR=mirabegron
[†]Expenditure for the last quarter (Q4) of 2015 was estimated based on the predicted number of users for this quarter.

Exhibit 90: Forecasted expenditure for OAB medications for patients aged 65 years or older.

YEAR	OAB MEDICATION EXPENDITURE (65+ yrs)							
ACTUAL	**DAR**	**FES**	**OXY**	**SOL**	**TOL**	**TRO**	**MYR**	**TOTAL**
2000	$0	$0	$2,121,623	$0	$2,444,480	$0	$0	$4,566,103
2001	$0	$0	$2,235,334	$0	$4,505,506	$0	$0	$6,740,840
2002	$0	$0	$2,336,897	$0	$6,011,099	$0	$0	$8,347,996
2003	$0	$0	$2,432,154	$0	$7,207,501	$0	$0	$9,639,655
2004	$0	$0	$2,537,187	$0	$9,201,953	$0	$0	$11,739,140
2005	$0	$0	$2,497,309	$0	$11,059,809	$0	$0	$13,557,118
2006	$0	$0	$2,452,185	$0	$13,191,857	$0	$0	$15,644,043
2007	$0	$0	$2,134,808	$0	$15,424,668	$0	$0	$17,559,475
2008	$0	$0	$1,998,610	$0	$17,099,190	$0	$0	$19,097,800
2009	$0	$0	$1,848,113	$0	$18,695,722	$0	$0	$20,543,835
2010	$0	$0	$1,548,759	$0	$20,500,391	$0	$0	$22,049,150
2011	$16,858	$0	$1,163,978	$53,397	$21,656,031	$2,133	$0	$22,892,397
2012	$1,101,059	$0	$1,044,874	$4,225,888	$20,472,793	$120,182	$0	$26,964,797
2013	$1,592,378	$786,849	$972,180	$7,576,620	$18,591,839	$203,128	$0	$29,722,994
2014	$1,852,118	$2,734,870	$881,038	$9,580,322	$16,054,380	$227,374	$0	$31,330,101
2015[†]	$1,950,701	$3,825,254	$800,428	$10,004,334	$13,923,956	$220,285	$4,008,829	$34,733,787
PREDICTED								
2016	$2,021,859	$3,808,827	$827,763	$2,585,654	$14,542,173	$233,951	$4,008,829	$28,029,056
2017	$2,119,690	$3,993,125	$867,816	$2,710,766	$15,245,825	$245,271	$4,008,829	$29,191,323
2018	$2,218,696	$4,179,633	$908,350	$2,837,378	$15,957,916	$256,727	$4,008,829	$30,367,530

Note: DAR=darifenacin, FES=fesoterodine, OXY=oxybutynin, SOL=solifenacin, TOL=tolterodine, TRO=trospium, MYR=mirabegron
[†]Expenditure for the last quarter (Q4) of 2015 was estimated based on the predicted number of users for this quarter.

Impact of Alternative Approaches to Reimbursement

As a result of the recent approval of mirabegron for coverage by OPDP (May 2015), consideration for alternative reimbursement options relating to this drug class was based on several groups of strategies relating to assumptions of either no change or different levels of change in mirabegron uptake and prescribing over the next three years. The same sets of strategies were considered for patients aged less than 65 years and for patients aged 65 years and older with overactive bladder symptoms.

When assuming no change in mirabegron prescribing from 2016 to 2018, enforced step therapy would lead to a 23% reduction in expenditure for patients aged less than 65 if it were assumed that patients would not increase their total time on all therapies (strategy 2a). If this was combined with an LU listing for Ditropan XL, Gelnique, and Oxytrol (strategy 2b), expenditure in the same group would decrease by 22% (Exhibit 91). A similar trend was observed among patients aged 65 years and older, with a 31% and 26% reduction in overall OAB medication expenditure generated by strategy 2a and strategy 2b, respectively (Exhibit 95).

However, when assuming no change in mirabegron prescribing from 2016 to 2018, enforced step therapy would lead to an 11% increase in expenditure for patients aged less than 65 if it were assumed that patients would not decrease their time on each therapy (strategy 3a). If this was combined with LU listing for Ditropan XL, Gelnique, and Oxytrol (strategy 3b) expenditure in the same group would increase by 18% (Exhibit 91). Similar trends were again observed among patients aged 65 years and older (Exhibit 95). Thus, the impact of enforced step therapy is unclear and may lead to increased expenditures.

A general benefit listing of tolterodine IR and solifenacin would lead to an increase in overall OAB medication expenditure (strategy 4a). Furthermore, if all those who would not take oxybutynin IR were assumed to take solifenacin (strategy 5a), there would be no impact on the forecasted expenditure in 2018 for persons aged less than 65 years; however, this strategy would lead to a 1% increase in projected spending among persons aged 65 years and older. Conversely, if all those taking oxybutynin IR were assumed to use solifenacin (strategy 5b), a 2% increase in overall OAB medication expenditure would be observed among all patient age groups by 2018 (Exhibit 91, Exhibit 95).

Where different levels of change in mirabegron prescribing were assumed with no other changes to the listing status of currently covered medications, an increase in mirabegron prescribing (either 10% or 20% per year) led to a small reduction (-1%) in overall OAB medication expenditure by the end of 2018 among patients aged less than 65 years (Exhibit 92). Among those aged 65 years and older, however, increased prescribing of mirabegron (either 10% or 20% per year) led to a 1% increase in overall expenditure by the end of the same term (Exhibit 96). Thus, increased use of mirabegron is unlikely to significantly increase overall OAB medication expenditure.

Assuming different levels of increase in mirabegron prescribing had little impact on the above conclusions with respect to the impact of enforced step therapy or general befit listing of tolterodine IR and solifenacin among all age groups (Exhibit 93, Exhibit 94, Exhibit 97, Exhibit 98).

Exhibit 91: Forecasted total costs (2018) under each alternative reimbursement strategy for patients aged less than 65 years (assuming no change in mirabegron prescribing).

AVERAGE COST OF OAB MEDICATIONS IN 2018					
REIMBURSEMENT STRATEGY	**ACh[1]**	**MYR[2]**	**TOTAL**	**NET BUDGET IMPACT**	**%**
#1a. Status quo (base case): No change to current GB listing for OXY IR and LU for currently covered agents					
	$5,516,841.03	$526,779.68	$6,043,620.71	N/A	N/A
#1b. 1a + LU listing for Ditropan XL, Gelnique, Oxytrol					
	$6,018,668.77	$526,779.68	$6,545,448.45	$501,827.74	8%
#2a. Enforced step therapy for ACh medications assuming no increase in overall time on all OAB agents					
	$4,193,726.02	$333,087.18	$4,526,813.20	-$1,516,807.51	-23%
#2b. 2a + LU listing for Ditropan XL, Gelnique, Oxytrol					
	$4,723,035.13	$333,087.18	$5,056,122.31	-$987,498.40	-22%
#3a. Enforced step therapy for ACh medications assuming no change in time on individual OAB therapy					
	$6,059,672.32	$526,779.68	$6,586,452.00	$542,831.29	11%
#3b. 3a + LU listing for Ditropan XL, Gelnique, Oxytrol					
	$6,694,899.93	$526,779.68	$7,221,679.61	$1,178,058.90	18%
#4a. GB listing for generic products (OXY IR, TOL IR, SOL) and LU listing for currently covered agents except TOL IR and SOL					
	$5,911,995.34	$526,779.68	$6,438,775.02	$395,154.31	5%
#4b. 4a + LU listing for Ditropan XL, Gelnique, Oxytrol					
	$6,409,842.86	$526,779.68	$6,936,622.54	$893,001.82	14%
#5a. GB listing for OXY and SOL and LU listing for all other currently covered agents					
	$5,541,872.30	$526,779.68	$6,068,651.98	$25,031.27	0%
#5b. GB listing for SOLF and LU listing for all other currently covered agents					
	$5,629,575.05	$526,779.68	$6,156,354.73	$112,734.02	**2%**

[1] ACh = Anticholinergic OAB medications, includes darifenacin (DAR), fesoterodine (FES), oxybutynin (OXY), solifenacin (SOL), tolterodine (TOL), and trospium (TRO)

[2] MYR = mirabegron (beta-3 adrenergic agonist)

Exhibit 92: Forecasted total costs (2018) under each alternative reimbursement strategy for patients aged less than 65 years (assuming different levels of change in mirabegron prescribing).

AVERAGE COST OF OAB MEDICATIONS IN 2018					
REIMBURSEMENT STRATEGY	**ACh[1]**	**MYR[2]**	**TOTAL**	**NET BUDGET IMPACT**	**%**
#1a. Status quo (base case): No change to current GB listing for OXY IR and LU for currently covered agents					
	$5,516,841.03	$526,779.68	$6,043,620.71	N/A	N/A
#1c. 1a + 10% increase in mirabegron use					
	$5,303,108.05	$701,143.75	$6,004,251.80	-$39,368.91	-1%
#1d. 1a + 20% increase in mirabegron use					
	$5,046,757.60	$910,275.29	$5,957,032.89	-$86,587.82	-1%

[1] ACh = Anticholinergic OAB medications, includes darifenacin (DAR), fesoterodine (FES), oxybutynin (OXY), solifenacin (SOL), tolterodine (TOL), and trospium (TRO)

[2] MYR = mirabegron (beta-3 adrenergic agonist)

Exhibit 93: Forecasted total costs (2018) under each alternative reimbursement strategy for patients aged less than 65 years (assuming 10% increase in mirabegron prescribing per annum).

AVERAGE COST OF OAB MEDICATIONS IN 2018					
REIMBURSEMENT STRATEGY	**ACh[1]**	**MYR[2]**	**TOTAL**	**NET BUDGET IMPACT**	**%**
#1c. Status quo (base case): No change to current GB listing for OXY IR and LU for currently covered agents + 10% increase in mirabegron use					
	$5,303,108.05	$701,143.75	$6,004,251.80	N/A	N/A
#2c.Enforced step therapy for ACh medications assuming no increase in overall time on all OAB agents + 10% increase in mirabegron use					
	$4,033,845.17	$443,339.04	$4,477,184.21	-$1,527,067.59	-25%
#3c. Enforced step therapy for ACh medications assuming no change in time on individual OAB therapy + 10% increase in mirabegron use					
	$5,827,501.14	$701,143.75	$6,528,644.89	$524,393.09	9%
#4c. GB listing for generic products (OXY IR, TOL IR, SOL) and LU listing for currently covered agents except TOL IR and SOL + 10% increase in mirabegron use					
	$5,682,953.32	$701,143.75	$6,384,097.07	$379,845.27	6%

[1] ACh = Anticholinergic OAB medications, includes darifenacin (DAR), fesoterodine (FES), oxybutynin (OXY), solifenacin (SOL), tolterodine (TOL), and trospium (TRO)

[2] MYR = mirabegron (beta-3 adrenergic agonist)

Exhibit 94: Forecasted total costs (2018) under each alternative reimbursement strategy for patients aged less than 65 years (assuming 20% increase in mirabegron prescribing per annum).

AVERAGE COST OF OAB MEDICATIONS IN 2018					
REIMBURSEMENT STRATEGY	**ACh[1]**	**MYR[2]**	**TOTAL**	**NET BUDGET IMPACT**	**%**
#1d. Status quo (base case): No change to current GB listing for OXY IR and LU for currently covered agents + 20% increase in mirabegron use					
	$5,046,757.60	$910,275.29	$5,957,032.89	N/A	N/A
#2d.Enforced step therapy for ACh medications assuming no increase in overall time on all OAB agents + 20% increase in mirabegron use					
	$3,842,084.76	$575,574.65	$4,417,659.41	-$1,539,373.48	-26%
#3d. Enforced step therapy for ACh medications assuming no change in time on individual OAB therapy + 20% increase in mirabegron use					
	$5,227,228.47	$910,275.29	$6,137,503.76	$180,470.87	3%
#4d. GB listing for generic products (OXY IR, TOL IR, SOL) and LU listing for currently covered agents except TOL IR and SOL + 20% increase in mirabegron use					
	$5,408,241.28	$910,275.29	$6,318,516.57	$361,483.68	6%

[1] ACh = Anticholinergic OAB medications, includes darifenacin (DAR), fesoterodine (FES), oxybutynin (OXY), solifenacin (SOL), tolterodine (TOL), and trospium (TRO)

[2] MYR = mirabegron (beta-3 adrenergic agonist)

Exhibit 95: Forecasted total costs (2018) under each alternative reimbursement strategy for patients aged 65 years and older (assuming no change in mirabegron prescribing).

AVERAGE COST OF OAB MEDICATIONS IN 2018					
REIMBURSEMENT STRATEGY	**ACh[1]**	**MYR[2]**	**TOTAL**	**NET BUDGET IMPACT**	**%**
#1a. Status quo (base case): No change to current GB listing for OXY IR and LU for currently covered agents					
	$26,358,700.77	$4,008,829.13	$30,367,529.91	N/A	N/A
#1b. 1a + LU listing for Ditropan XL, Gelnique, Oxytrol					
	$27,499,303.63	$4,008,829.13	$31,508,132.76	$1,140,602.86	4%
#2a. Enforced step therapy for ACh medications assuming no increase in overall time on all OAB agents					
	$18,358,308.98	$2,534,816.06	$20,893,125.04	-$9,474,404.87	-31%
#2b. 2a + LU listing for Ditropan XL, Gelnique, Oxytrol					
	$19,953,114.16	$2,534,816.06	$22,487,930.21	-$7,879,599.69	-26%
#3a. Enforced step therapy for ACh medications assuming no change in time on individual OAB therapy					
	$28,437,605.60	$4,008,829.13	$32,446,434.74	$2,078,904.83	7%
#3b. 3a + LU listing for Ditropan XL, Gelnique, Oxytrol					
	$30,306,518.10	$4,008,829.13	$34,315,347.23	$3,947,817.33	13%
#4a. GB listing for generic products (OXY IR, TOL IR, SOL) and LU listing for currently covered agents except TOL IR and SOL					
	$28,076,599.85	$4,008,829.13	$32,085,428.98	$1,717,899.08	6%
#4b. 4a + LU listing for Ditropan XL, Gelnique, Oxytrol					
	$29,148,711.83	$4,008,829.13	$33,157,540.97	$2,790,011.06	9%
#5a. GB listing for OXY and SOL and LU listing for all other currently covered agents					
	$26,715,003.85	$4,008,829.13	$30,723,832.99	$356,303.08	**1%**
#5b. GB listing for SOLF and LU listing for all other currently covered agents					

AVERAGE COST OF OAB MEDICATIONS IN 2018					
REIMBURSEMENT STRATEGY	**ACh[1]**	**MYR[2]**	**TOTAL**	**NET BUDGET IMPACT**	**%**
	$27,038,332.72	$4,008,829.13	$31,047,161.85	$679,631.94	2%

[1] ACh = Anticholinergic OAB medications, includes darifenacin (DAR), fesoterodine (FES), oxybutynin (OXY), solifenacin (SOL), tolterodine (TOL), and trospium (TRO)
[2] MYR = mirabegron (beta-3 adrenergic agonist)

Exhibit 96: Forecasted total costs (2018) under each alternative reimbursement strategy for patients aged 65 years and older (assuming different levels of change in mirabegron prescribing).

AVERAGE COST OF OAB MEDICATIONS IN 2018					
REIMBURSEMENT STRATEGY	**ACh[1]**	**MYR[2]**	**TOTAL**	**NET BUDGET IMPACT**	**%**
#1a. Status quo (base case): No change to current GB listing for OXY IR and LU for currently covered agents					
	$26,358,700.77	$4,008,829.13	$30,367,529.91	N/A	N/A
#1c. 1a + 10% increase in mirabegron use					
	$25,218,665.65	$5,335,751.58	$30,554,417.23	$186,887.33	1%
#1d. 1a + 20% increase in mirabegron use					
	$23,851,312.36	$6,927,256.74	$30,778,569.10	$411,039.20	1%

[1] ACh = Anticholinergic OAB medications, includes darifenacin (DAR), fesoterodine (FES), oxybutynin (OXY), solifenacin (SOL), tolterodine (TOL), and trospium (TRO)
[2] MYR = mirabegron (beta-3 adrenergic agonist)

Exhibit 97: Forecasted total costs (2018) under each alternative reimbursement strategy for patients aged 65 years and older (assuming 10% increase in mirabegron prescribing per annum).

AVERAGE COST OF OAB MEDICATIONS IN 2018					
REIMBURSEMENT STRATEGY	**ACh[1]**	**MYR[2]**	**TOTAL**	**NET BUDGET IMPACT**	**%**
#1c. Status quo (base case): No change to current GB listing for OXY IR and LU for currently covered agents + 10% increase in mirabegron use					
	$25,218,665.65	$5,335,751.58	$30,554,417.23	N/A	N/A
#2c.Enforced step therapy for ACh medications assuming no increase in overall time on all OAB agents + 10% increase in mirabegron use					
	$18,358,308.98	$3,373,840.17	$21,732,149.15	-$8,822,268.08	-29%
#3c. Enforced step therapy for ACh medications assuming no change in time on individual OAB therapy + 10% increase in mirabegron use					
	$28,437,605.60	$5,335,751.58	$33,773,357.18	$3,218,939.95	11%
#4c. GB listing for generic products (OXY IR, TOL IR, SOL) and LU listing for currently covered agents except TOL IR and SOL + 10% increase in mirabegron use					
	$26,862,264.21	$5,335,751.58	$32,198,015.79	$1,643,598.56	5%

[1] ACh = Anticholinergic OAB medications, includes darifenacin (DAR), fesoterodine (FES), oxybutynin (OXY), solifenacin (SOL), tolterodine (TOL), and trospium (TRO)
[2] MYR = mirabegron (beta-3 adrenergic agonist)

Exhibit 98: Forecasted total costs (2018) under each alternative reimbursement strategy for patients aged 65 years and older (assuming 20% increase in mirabegron prescribing per annum).

AVERAGE COST OF OAB MEDICATIONS IN 2018					
REIMBURSEMENT STRATEGY	**ACh[1]**	**MYR[2]**	**TOTAL**	**NET BUDGET IMPACT**	**%**
#1d. Status quo (base case): No change to current GB listing for OXY IR and LU for currently covered agents + 20% increase in mirabegron use					
	$23,851,312.36	$6,927,256.74	$30,778,569.10	N/A	N/A
#2d.Enforced step therapy for ACh medications assuming no increase in overall time on all OAB agents + 20% increase in mirabegron use					
	$18,358,308.98	$4,380,162.14	$22,738,471.13	-$8,040,097.97	-26%
#3d. Enforced step therapy for ACh medications assuming no change in time on individual OAB therapy + 20% increase in mirabegron use					
	$28,437,605.60	$6,927,256.74	$35,364,862.35	$4,586,293.25	15%
#4d. GB listing for generic products (OXY IR, TOL IR, SOL) and LU listing for currently covered agents except TOL IR and SOL + 20% increase in mirabegron use					
	$25,405,795.18	$6,927,256.74	$32,333,051.92	$1,554,482.82	5%

[1] ACh = Anticholinergic OAB medications, includes darifenacin (DAR), fesoterodine (FES), oxybutynin (OXY), solifenacin (SOL), tolterodine (TOL), and trospium (TRO)
[2] MYR = mirabegron (beta-3 adrenergic agonist)

Overall Conclusions

In brief, without any changes to current reimbursement for OAB medications and the expected availability of generic solifenacin by the end of 2015, OAB medication expenditure is expected to decrease to $6.0 million for patients aged less than 65 years and to $30.4 million for patients aged 65 years and older by the end of 2018. Furthermore, assuming no change in mirabegron prescribing over the next three years, enforcement of step therapy for anticholinergic medications would generate a reduction in overall OAB medication expenditure (-23% patients younger than 65 years; -31% for patients 65 years and older) if this did not lead to an increase in time on all therapies (strategy 2a). However, enforcement of step therapy for anticholinergic medications would generate an increase in overall OAB medication expenditure if there was no change in time on individual therapies (strategy 3a). A strategy whereby oxybutynin and solifenacin are listed as general benefit with a limited use listing for all other currently covered agents (strategy 5a) or a general benefit listing for solifenacin with all other agents on limited use (strategy 5b) would not lead to a decrease in expenditure for OAB medications by the end of 2018.

If mirabegron prescribing were to increase by either 10% or 20% per annum from 2016 to 2018, there would be limited effect on overall OAB medication expenditure if there were no change to current coverage. If mirabegron expenditure increased, enforcement of step therapy for anticholinergic agents with no increase in time on all therapies (strategy 2d) would still generate a reduction in overall OAB medication expenditure by the end of 2018, though the reduction will be slightly smaller.

Appendix C1: Model Details

Exhibit 99: Model details for anticholinergic agents and mirabegron for OAB patients aged less than 65 years.

	MIRABEGRON	NO. DRUGS IN CLASS	QUARTER	CONSTANT
LINEAR MODEL				
Coefficient	-1621.028462	194.03	573.6509359	2765.805177
Std. error	383.8168051	16.91	5.822931055	37.37728724
BIC	5009.89021			
	MIRABEGRON	**NO. DRUGS IN CLASS**	**QUARTER**	**CONSTANT**
EXPONENTIAL MODEL				
Coefficient	0.73667891	0.98	1.092741667	3884.333148
Std. error	0.07902745	0.00	0.001198935	0.007695942
BIC	4572.914037			
	MIRABEGRON	**NO. DRUGS IN CLASS**	**QUARTER**	**CONSTANT**
POWER MODEL				
Coefficient	-4761.813257	-353.35	44.17894372	5273.832139
Std. error	1049.587317	58.84	1.241796662	104.5191718
BIC	4671.060544			
	MIRABEGRON	**NEW TRT AVAILABLE**	**CONSTANT**	
CONSTANT GROWTH MODEL				
Coefficient	-0.130963807	-0.003838921	0.021577831	
Std. error	0.029697128	0.005215799	0.001088905	
BIC	4513.012194			

Exhibit 100: Model details for anticholinergic agents and mirabegron for OAB patients aged 65 years and older.

	MIRABEGRON	NO. DRUGS IN CLASS	QUARTER	CONSTANT
LINEAR MODEL				
Coefficient	-5617.625121	561.98	1985.905917	18335.56872
Std. error	2666.810247	117.49	40.45849998	259.7023666
BIC	4713.426295			
	MIRABEGRON	**NO. DRUGS IN CLASS**	**QUARTER**	**CONSTANT**
EXPONENTIAL MODEL				
Coefficient	0.806452103	0.99	1.067922168	21261.35746
Std. error	0.128494214	0.01	0.001949401	0.012513171
BIC	4738.511668			
	MIRABEGRON	**NO. DRUGS IN CLASS**	**QUARTER**	**CONSTANT**

	MIRABEGRON	NO. DRUGS IN CLASS	QUARTER	CONSTANT
POWER MODEL				
Coefficient	-7335.898676	199.57	1126.784482	20753.70645
Std. error	3444.394849	159.60	29.86638482	321.881771
BIC	4753.321604			
	MIRABEGRON	**NEW TRT AVAILABLE**	**CONSTANT**	
CONSTANT GROWTH MODEL				
Coefficient	-0.129289771	0.01138847	0.016745433	
Std. error	0.04263645	0.007488372	0.001563351	
BIC	4761.998532			

Appendix D – Reimbursement-based Economic Evaluation

Research Question

RQ4. Based on a de novo economic model, what is the cost-effectiveness of alternative policies for reimbursing pharmacologic treatments for OAB syndrome?

Methods

Initial analysis considered the reimbursement strategies considered within the budget impact analysis. (Exhibit 101).

Exhibit 101: Initial Strategies considered within the reimbursement-based economic analysis

	Strategy
1a.	Status quo: no change. General benefit (GB): oxybutynin IR Limited use (LU): currently covered agents (DAR, FES, SOL, TOL, TRO, MYR, BTX)
1b.	Same as 1a EXCEPT: LU listing for Ditropan XL, Gelnique, Oxytrol
2a.	ENFORCED STEP THERAPY : assume no increase in total time on OAB agents General benefit (GB): oxybutynin IR Limited use (LU): currently covered agents
2b.	ENFORCED STEP THERAPY : assume no increase in total time on OAB agents Same as 2a EXCEPT: LU listing for Ditropan XL, Gelnique, Oxytrol
3a.	ENFORCED STEP THERAPY : assume no change in time on OAB agents General benefit (GB): oxybutynin IR Limited use (LU): currently covered agents
3b.	ENFORCED STEP THERAPY : assume no change in time on OAB agents Same as 3a EXCEPT: LU listing for Ditropan XL, Gelnique, Oxytrol
4a.	GB listing for generic products including oxybutynin, tolterodine IR, and solifenacin. LU listing for currently covered agents except tolterodine IR and solifenacin
4b.	Same as 4a EXCEPT: LU listing for Ditropan XL, Gelnique, Oxytrol

For the base analysis, we assumed both no increase in mirabegron prescribing and no change in time on OAB agents (strategies 3a and 3b). Sensitivity analysis considered both a 10% annual increase in mirabegron prescribing and that step therapy would lead to no increase in total time on OAB agents (strategies 2a and 2b).

Data from the de novo economic model were used to facilitate estimation of the costs and QALYs per quarter for each therapy assuming full compliance. This was based on estimating the time on each therapy based on the discontinuation rates and the costs per quarter for the initial quarter and subsequent quarters. The estimated costs and QALYs per quarter for each OAB therapy assuming full compliance are presented in Exhibit 102.

Exhibit 102: Costs and QALYs per quarter assuming full compliance

	QALYs	Costs
No therapy	0.170906	$0.00
Oxybutynin IR	0.173595	$40.50
Oxybutynin ER	0.175162	$153.91
Tolterodine ER	0.174115	$127.62
Tolterodine IR	0.174110	$127.61
Solifenacin	0.174753	$40.02
Fesoterodine	0.174265	$101.29
Trospium	0.174902	$84.43
Mirabegron	0.174463	$89.01
Darifenacin	0.173971	$110.56
Oxybutynin transdermal	0.174264	$111.83
Oxybutynin gel	0.174407	$102.75

Costs and QALYs for each strategy were estimated by weighting the estimated costs and QALYs for each therapy by their market share based on the assumptions within the budget impact analysis. (see Appendix C – Budget Impact Analysis)

The results of the de novo economic modelling found solifenacin to be cost effective compared to all other therapies. Thus, further analysis was conducted including two additional scenarios (GB listing for solifenacin and solifenacin included as fist line therapy within step therapy). (Exhibit 103)

Exhibit 103: Further strategies considered within the reimbursement-based economic analysis

	Strategy[†]
5a.	GB listing for oxybutynin, and solifenacin. LU listing for currently covered agents except solifenacin
6a.	ENFORCED STEP THERAPY : assume no increase in total time on OAB agents General benefit (GB): oxybutynin IR, solifenacin Limited use (LU): other currently covered agents
7a.	ENFORCED STEP THERAPY : assume no change in time on OAB agents General benefit (GB): oxybutynin IR, solifenacin Limited use (LU): currently covered agents

[†]For the further analysis costs and QALYs were estimated based on the same approach as the initial analysis.

Results

In the base analysis, the strategy of enforcing step therapy (i.e. using oxybutynin IR as first line therapy) would be cost effective compared to the other strategies considered. The incremental cost per QALY gained for this strategy versus status quo was $15,062. All other strategies were subject to dominance or extended dominance (Exhibit 104).

Exhibit 104: Base case results of reimbursement-based economic evaluation

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
Strategy 1	0.17257	$41.07		
Strategy 3a	0.17298	$47.21	$15,062	$15,062.27
Dominated				
Strategy 4a	0.17259	$41.85	$46,167	Subject to extended dominance through Strategies 1 and 3a
Strategy 1a	0.17257	$41.87	$1,289,105	Dominated by Strategy 4a
Strategy 4b	0.17259	$42.61	$92,246	Dominated by Strategy 4a
Strategy 3b	0.17296	$47.70	$17,096	Dominated by Strategy 3a

This was robust within sensitivity analysis when assuming a 10% increase in mirabegron prescribing (Exhibit 105)

Exhibit 105: Results of Sensitivity Analysis assuming 10% annual increase in mirabegron prescribing (2016-18)

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
Strategy 1	0.17258	$41.27		
Strategy 3a	0.17299	$47.49	$15,312	$15,312.09
Dominated				
Strategy 4a	0.17262	$42.96	$42,388	Subject to extended dominance through Strategies 1 and 3a
Strategy 1a	0.17258	$42.06	$143,094	Dominated by Strategy 4a
Strategy 4b	0.17261	$43.66	$60,342	Dominated by Strategy 4a
Strategy 3b	0.17297	$47.97	$17,288	Dominated by Strategy 3a

The results changed when assuming no total time on OAB agents. The strategy of step therapy now dominated the status quo. The strategy of moving solifenacin and tolterodine ER to general benefit was more effective than step therapy but was not cost effective with an ICER of $70,116 per QALY gained (Exhibit 106). Thus, the interpretation of the results was consistent across sensitivity analysis.

Exhibit 106: Results of Sensitivity Analysis assuming no change in total time on OAB agents

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
Strategy 2a	0.17246	$32.71		
Strategy 4a	0.17259	$41.85	$70,116	$70,115.85
Dominated				
Strategy 2b	0.17246	$33.92	$193,303.79	Subject to extended dominance through Strategies 2a and 4a
Strategy 1	0.17257	$41.07	$73,689.58	Subject to extended dominance through Strategies 2a and 4a
Strategy 1a	0.17257	$41.87	$80,287.12	Dominated by Strategy 4a
Strategy 4b	0.17259	$42.61	$76,070.88	Dominated by Strategy 4a

When the analysis was expanded to include two additional strategies, results revealed that the strategy whereby solifenacin and oxybutynin IR were considered as first line therapies with enforcement of step therapy was optimal. This strategy dominated the status quo and was cost effective compared to the strategy of simply moving solifenacin to GB with an ICER of $11,793 per QALY gained. Although strategy 3a was more effective, its ICER,as compared with strategy 7a, was over $7 million suggesting strategy 7a was optimal (Exhibit 107).

Exhibit 107: Revised results of reimbursement-based economic evaluation

	QALYs	Cost	Incremental cost per QALY gained vs. lowest cost	Sequential incremental cost per QALY gained
Not dominated				
Strategy 5a	0.17258	$41.06		
Strategy 7a	0.17298	$45.72	$11,792.86	$11,792.86
Strategy 3a	0.17298	$47.21	$15,542.91	$7,684,669.91
Dominated				
Strategy 4a	0.17259	$41.85	$169,091.54	Subject to extended domiannce through Strategies 5a and 7a
Strategy 1	0.17257	$41.07	Dominated by Strategy 5a	Dominated by Strategy 5a
Strategy 1a	0.17257	$41.87	Dominated by Strategy 5a	Dominated by Strategy 5a
Strategy 4b	0.17259	$42.61	$349,323.18	Dominated by Strategy 4a
Strategy 3b	0.17296	$47.70	$17,668.61	Dominated by Strategy 3a

Results were consistent within sensitivity analyses with step therapy including oxybutynin IR or solifenacin optimal. When assuming a ten per cent increase in mirabegron prescribing the ICER for strategy 7a versus 5a was $11,496 and strategy 7a dominated strategy 3a. When assuming no increase in total time on OAB agents, strategy 6a dominated all other strategies.

Conclusions

Initial analysis supported a policy of enforcing step therapy whereby patients must first take oxybutynin IR before allowing reimbursement for other currently covered OAB therapies. Analysis did not support moving solifenacin and tolterodine IR to general benefit nor did it support moving oxybutynin ER, tolterodine ER and oxybutynin gel to LU.

Given the results of the de novo modelling, further strategies relating to solifenacin were considered. This analysis suggests the enforcement of step therapy whereby oxybutynin IR or solifenacin are considered first line therapy is the optimal reimbursement strategy.

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